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Examining the Impact of Computer-Aided Clinical Decision Support on Antibiotic Use in Hospitals

**A thesis submitted to the University of
Birmingham for the degree of Doctor of
Philosophy in the College of Medical and
Dental Sciences**

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List of Abbreviations

A&E= Accident and Emergency department

AMR= Antimicrobial Resistance

BNF= British National Formulary

CDC= Centre for Disease Control

CDDEP= Centre for Disease Control and Prevention

CDSS = Computerised Decision Support System(s), can be plural or singular depending on the context

CPOE = Computerised Physician Order Entry

EHR = Electronic Health Record

e-Rx = Electronic Prescribing

ESPAUR= English Surveillance Programme for Antimicrobial Use and Resistance

HIT= Health Information Technology

NHS = National Health System

NPfIT= National Programme for Information Technology

PICS = Patient Information and Communication System

SSTF= Start Smart Then Focus

TARGET= Treat Antibiotics Responsibly, Guidance, Education, Tools

UHBFT= University Hospitals Birmingham Foundation Trust

UK= United Kingdom

US= United States of America

WHO = World Health Organisation

Abstract

Computerised clinical decision support systems (CDSS) are information technology tools used to optimise the use of antibiotics.

A systematic review and meta-analysis was conducted to review the level of evidence of the impact of CDSS on antibiotic prescribing using specific outcome measures. Overall, CDSS interventions were associated with an increase in adequacy of antibiotic coverage based on a random effects model [OR = 2.11, 95% CI, 1.67 to 2.66, $p < 0.00001$]. Results showed that CDSS had a marginal statistically significant effect on mortality based on a random effects model. [OR = 0.85, 95% CI, 0.75 to 0.96, $p = 0.01$].

Medical and non-medical healthcare professionals in University Hospitals Birmingham Foundation Trust were surveyed about their perceptions and attitudes towards CDSS. 85% participants showed a positive attitude towards CDSS.

A quantitative retrospective before-and-after study in the University Hospitals Birmingham Foundation Trust was conducted from June 2012 to June 2016 to measure the impact of a CDSS tool known as Structured Prescribing on the volume of antibiotic use. From June 2012 to June 2016, the total antibiotic usage increased by 13.1% from 1436.3 to 1624.85 DDD/1000 bed-days.

CDSS show demonstrable potential in optimising the use of antibiotics and containing antimicrobial resistance.

Keywords: Computerised clinical decision support systems, Structured prescribing, defined daily doses, hospitals.

Declaration

No portion of the work referred to in the thesis has been submitted in support of an application for another or qualification of this or any other university or other institute of learning

Dedication

To my lovely wife Lina Alawi and my little daughter Layan

Thank you all for your love and kindness

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Abstracts

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Al Bahar, F., Marriott, J. F., Curtis, C. E. 'Exploring the preceptions and attitudes of medical and non-medical healthcare professionals towards computerised decision support systems: a questionnaire' (Poster discussion forum at the Royal Pharmaceutical Society conference, September, 2016, Birmingham).

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Chapter 1: Introduction

1.1 Introduction

This introductory chapter gives an overview of the background and context to the research and the drivers that led to the development of research questions, aims and objectives. This chapter covers the following areas:

- An overview of clinical decision making and prescribing of medications.
- Antimicrobial resistance (AMR), its clinical and economic burden, and its key drivers.
- Patterns and trends of antibiotic resistance and antibiotic consumption are explored in England and globally.
- Local, regional and international governmental and non-governmental strategies and antimicrobial management initiatives to address AMR and inappropriate antimicrobial prescribing are discussed.
- The concept of antimicrobial stewardship.
- Health information technology (HIT) interventions, namely Electronic prescribing (e-Rx) and clinical decision support systems (CDSS), and their impact in optimising antibiotic use, improving practitioner performance, and patient outcomes.

1.2 Statement of the problem

Antimicrobial prescribing in secondary care has been at the core of debate for many years. The decision to prescribe antimicrobials is a dynamic process and dependent on unorganised and untimely information (Holstiege et al., 2015). Given the inconsistency of means used for retrieving important clinical information at the patient-physician interface, clinical knowledge needs are often not successfully matched in a real-time fashion (Thursky, 2006). Therefore, clinicians depend on their largely non-modifiable human memory in making decisions because of the inefficiency of traditional information storage and delivery systems (Bero et al., 1998, Buchan, 2004, Thursky, 2006).

Antimicrobial choice is not a simple issue in medical practice owing to its impact on the development of antimicrobial resistance (AMR) (Holstiege et al., 2015). Evidence-based guidelines are the gold standard for decision-making by prescribers. However, non-compliance of clinicians with standard guidelines is very common explaining the evidence-practice chasm (Thursky, 2006). This non-compliance could be due to the lack of awareness of doctors of the availability of guidelines or even the inability to check them owing to their busy work schedule. Prescribers may be autonomous believing that they know the best antimicrobial choice in a specific situation, or they may be unconvinced that their choice is irrational. Many doctors are reluctant to refuse to give antimicrobial therapy if the diagnosis is uncertain, or to take the risk of treatment failure by avoiding broad-spectrum antimicrobials. The duration of antimicrobial treatment is often longer than required (Leekha, Terrell et al. 2011) because no stop date is stated in drug orders and there can be failure to cancel or review them (Duguid and Cruickshank, 2010). Deciding on the duration of antibiotic treatment is not straightforward. Most recommendations in infectious diseases guidelines are based on expert opinions and evidence based medicine. A short or a long course of antibiotics can be given to patients depending on the severity of infection, drug used and response to the treatment. Shortening antimicrobial therapy is an important strategy to optimise patient care and reduce the development of resistance. Many patients with hospital acquired pneumonia, ventilator associated pneumonia and health care associated pneumonia can be treated for 7-10 days. While patients with intra-abdominal infections can be treated for 4-7 days and patients with catheter related blood stream infections can be treated for 14 days (File, 2012).

In the United Kingdom, it has been reported that the quality of antimicrobial prescribing is sub-optimal and that there is a gap between the optimal standard and the actual practice (Martin et al., 2003, Klein, 2004). This gap can lead to serious complications for health services and patient safety. These consequences may be in the form of infection misdiagnosis,

antimicrobial-related errors, increased complications for patients with infections, hospital admission owing to antimicrobial adverse drug reactions, and outbreak of infectious diseases such *Clostridium difficile*. This gap also exacerbates the financial burden on healthcare systems and governments by increasing hospital admission rates and lengths of hospital stay owing to difficult to treat infections (Hitchen, 2006, Davies et al., 2010).

Mounting evidence of the burden of AMR and infections has informed a number of strategic reports and national policy on containing AMR and optimising the rationale use of antimicrobial agents. The desperate need for comprehensive solutions has been highlighted to develop and implement health systems that will facilitate the safe and effective use of antimicrobials. Health Information Technology (HIT) has been shown to be a promising solution in facilitating the redesign of such health care systems (Sheikh et al., 2011). Health care professionals' engagement in HIT strategies, such as the use of CDSS is therefore a key area of interest for those involved in optimising antimicrobial use and the containment of AMR.

The system for prescribing medications in the UK has not changed for the last five decades (NHS Connecting for Health, 2009). The increasing number and complexity of medications has possibly increased the risk of medication errors. For UK secondary care, medications are prescribed using a system developed 50-60 years ago. Prescribers write paper-based prescriptions which are then usually checked by nurses and pharmacists for suitability, accuracy and compatibility. Evidence has shown that more than 3% of prescriptions contained an error of drug use and more than 30% an error in prescription writing (Tesh and Beeley, 1975). Dean and co-workers found that prescribing errors occurred in 1.5% of medication orders (Dean et al., 2002). Potentially serious errors occurred in 0.4% of medication orders. A study by Franklin and co-workers showed that 9.2% of medication orders contained at least one prescribing error (Franklin et al., 2007). It shows that the incidence of prescribing increased in later years supporting the need for CDSS.

The UK health care system is confronted with several challenges, including the rapid expanding nature of medical information together with formulary and clinical practice policies. It is difficult to overcome this issue as relevant medical information may be scattered across different databases within an organization. It is therefore unlikely that clinicians can optimally retrieve the necessary information required to inform their decisions and optimise the quality of patient care (Calloway et al., 2013). Antimicrobial prescribing in secondary care is an example of such a dilemma where decisions rely on uncertain and unstructured information obtained from different databases.

1.3 Background

1.3.1 Antimicrobials and modern medicine

Antimicrobials have saved millions of lives since their introduction in the 1940s through their role in treating microbial diseases effectively. Their role has gone beyond treating life-threatening infections to include surgical prophylaxis, protecting oncology patients and immunocompromised patients, and in promoting growth and preventing disease in livestock and other food animals (Center for Disease Dynamics, Economics & Policy, 2015). However, easily managed infections are becoming difficult to treat, are increasing healthcare costs and compromising patient safety. In 2002, it was estimated that the annual economic costs of the prevention and management of infections at U.S. hospitals were \$ 6.7 billion (Graves, 2004), and £1.06 billion in the United Kingdom (Plowman et al., 2001, Graves, 2004). Also, it has been estimated that antimicrobial related costs are up to one half of a health care institution's budget (Santell, 1995, Pestotnik et al., 1996). In England, consultation with health care professional are made for 40 % of the population every year, and almost 150,000 people are admitted to a hospital because of infection complications (Shebl et al., 2007).

Use of antimicrobial agents has become more prevalent and these drugs have been misused in both humans and food-producing animals in a way that has driven the selection of resistant

pathogens. This irrational use has led to a decline, or even loss of their antimicrobial activity at an alarming rate resulting in a global health emergency that is rapidly surpassing available treatment choices. Many microbes are resistant to more than one antimicrobial agent, and broad-spectrum antimicrobials are not affordable and often not available in regions with limited economic resources (Center for Disease Dynamics, Economics & Policy, 2015). To keep this magic bullet effective, it is essential to conserve the efficacy of current antimicrobial agents through measures that limit the development and spread of resistance while endeavours to develop new antimicrobial agents continue.

The pipeline for the development of new antimicrobial agents has reduced significantly and research to develop new antimicrobial agents takes time. Some pathogens are becoming resistant to most or in some cases all current antimicrobial agents and are causing difficult-to-treat infections that were easily managed in the past. Consequently, modern medicine is under threat evidenced by the following situations (World Health Organisation, 2001):

- i. Common community-acquired infections may become unresponsive to current antimicrobial agents.
- ii. Some urinary tract infections, such as cystitis, may not respond to oral treatment and may require treatment with parenteral therapy.
- iii. Infections in intensive care units are becoming less easily managed or even impossible to treat.
- iv. Failure to treat infections in immunocompromised patients such as patients receiving chemotherapy or organ transplant may put patients at risk
- v. Declining or lack of effectiveness of antimicrobial agents used to treat post-surgical infections

1.3.2 Antimicrobial resistance

The rapid emergence of resistant bacterial is happening worldwide compromising the efficacy of existing antibiotics (Ventola, 2015). After the passage of time of treating patients with infections with antibiotics, bacterial infections have again become a threat. The emergence of bacterial resistance has been attributed to the misuse and over use of antibiotics (Ventola, 2015).

The introduction of penicillin more than 70 years ago was one of the greatest achievements of health care in history. However, penicillin has been rendered ineffective by the ability of bacteria to acquire resistance (Abraham and Chain, 1988). Since 1940 many new antimicrobial agents have been discovered and have later become ineffective owing to the ability of pathogens to develop resistance. The excessive use of antimicrobial agents increases selection pressure that favours the survival and growth of pathogens that are resistant to their mode of action.

AMR is the ability of microorganisms to resist the effect of drugs by not being killed or their growth is not affected (World Health Organization web page, 2014). Resistant pathogens including bacteria, viruses, fungi and parasites are able to tolerate attack by antimicrobial agents such as antibacterial, antifungal, antiviral, and antimalarial agents.

The emergence of resistance to *Mycobacterium tuberculosis*, which caused many fatalities in England in the 18th and 19th centuries, is now considered a real threat to the public health across Europe (El-Nemr, 2014). Similarly, resistance to gonorrhoea is emerging to both penicillins and ciprofloxacin and leaving cephalosporins- though reduction in their susceptibility- the standard treatment with no available alternate therapy (Chisholm et al., 2010). AMR is problematic especially with untreatable infections caused by resistant pathogens known as the "ESKAPE" (see table 1) (Rice, 2008). For example, Gram-negative bacteria Enterobacteriaceae such as *E. coli* and *Klebsiella*, which are now the most frequent cause of

hospital-acquired infections, are becoming more problematic owing their emerging resistance behaviour (Health Protection Agency, 2011).

Table 1: Bad bacteria ESKAPE pathogens

Gram positive <i>Enterococcus faecium</i> <i>Staphylococcus aureus</i>	Gram negative <i>Klebsiella species</i> <i>Acinetobacter baumannii</i> <i>Pseudomonas aeruginosa</i> <i>Enterobacter species</i> and <i>Escherichia coli</i>
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Adapted from Rice 2008

AMR is not a new phenomenon and was first mentioned by Sir Alexander Fleming in his Nobel Lecture in 1945. He stated that the suboptimal dosing and excessive use of antibiotics was the main driver for AMR. However, the rapid escalation of AMR and the extent of the problem raises public health concerns of this situation. There is a possibility of a future without any effective antimicrobial agents to treat common infections. Additionally, the dearth of new antimicrobial agents limits treatment choices especially for multi-drug resistant pathogens. The development of new antimicrobial agents will not be sufficient to contain AMR as pathogens will continue to develop ways to withstand their effect. Therefore, preserving the efficacy of existing antimicrobial agents via promoting their rational use is paramount to reduce selection pressure that results in the development of AMR.

1.3.2.1 Basis of resistance

Different classes of antimicrobial agents have different mechanisms of action by which they inhibit the growth of or kill pathogenic organisms. These range from the inhibition of cell wall synthesis and inhibition of protein synthesis to inhibition of DNA synthesis and inhibition of folic acid synthesis. All of these mechanisms of action include the binding of antimicrobials to a specific target site within the microorganisms (Department of Health and Public Health England, 2015). Therefore, pathogens can acquire resistance by preventing antimicrobials binding to their sites of action. There are a number of mechanisms by which pathogens develop

resistance to antimicrobials including mutation, gene transfer or by the selection of inherently resistant species (Department of Health, 1998). The significance of these individual mechanisms differs with the type of pathogen, the antimicrobial agent and the clinical setting. The excessive use of antimicrobial agents increases the selection pressure that favours the survival and growth of micro-organisms that are resistant to their action.

1.3.2.2 Mutation

Mutations are random genetic changes that confer the ability to acquire resistance by a number of mechanisms specifically (Department of Health, 1998):

- I. Increasing the rate antimicrobial agent degradation
- II. Reducing the ability of the antimicrobial agent to enter into the cell
- III. Increasing the rate of antimicrobial agent efflux
- IV. Changing the antimicrobial agent's target binding site
- V. Alteration of the metabolic pathway of the antimicrobial agent

The dominance of a single mutant gene within a population of bacteria can lead to development of a population of resistant bacteria. Therefore, failure of therapy will result if resistant mutant bacteria are selected (Andersson and Hughes, 2017)

1.3.2.3 Gene transfer

Genetic information may be exchanged between bacteria by different mechanisms including via plasmids, separate circular DNA fragments from the chromosome, which carry resistant genetic fragments known as transposons. They can transfer from one plasmid to another and even to chromosomes maximizing their ability to spread (Andersson and Hughes, 2017). Several resistance genes, which may be carried via plasmids, encode for antibiotic-destroying enzymes, target changing enzymes, and drug efflux pumps. Resistant microorganisms have the ability to share their DNA with other microbes via conjugation (passage of plasmids between

cells), transduction (DNA transfer via a bacteriophage), and transformation (uptake of DNA when cells die).

1.3.2.4 Inherently resistant species

Inherently resistant pathogens are commonly seen in hospitals especially in patients who are vulnerable to opportunistic pathogen (Peleg and Hooper, 2010). The irrational use of some antibiotics promotes the development of resistance to microorganisms. For example, sub-optimal use of cephalosporins and quinolones has been reported to be implicated in the development of resistance in *Enterococci* species which were originally susceptible (Woodford et al., 1995). Normal flora may be harmed by antimicrobial chemotherapy which leads to increased numbers of pathogenic bacteria such as *Clostridium difficile*.

1.3.2.5 Multi-resistance

Multi-resistance is the resistance of a pathogen to more than one antimicrobial agent. New strains of *Mycobacterium tuberculosis* have emerged which are resistant to key therapeutic treatments, known as multi-drug resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) (Abubakar et al., 2012). Methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococci* (VRE) are not only resistant to methicillin and vancomycin, respectively, but also to other alternative antimicrobial agents. Multi-resistance may be explained by the presence of single plasmids encoding diverse resistance mechanisms, or by efflux systems that confer the ability to pump out multiple drugs (Department of Health, 1998).

1.4 Practices that predispose to sub-optimal antibiotic prescribing and the development of AMR

Health care professionals, health care settings and patients all play an integral role in the evolution and spread of AMR. It has been suggested that AMR is mainly caused by non-human use of antimicrobials, such as in veterinary medicine and growth promotion in food producing

animals (Department of Health, 1998). However, given the widespread of resistance to antimicrobials that have never been used in non-human (eg. ceftriaxone) and for pathogens that are specific to human (eg. *Streptococcus pneumonia*) there may be additional factors involved (Department of Health, 1998).

1.4.1 Total antibiotic consumption

It has been shown that high use of antimicrobial agents may be correlated with greater rates of resistance (Department of Health, 1998). Resistance and consumption rates of antimicrobial agents differ from country to country. In 2010, the three countries that had the highest rates of consumption were India, China and the United States (Van Boeckel et al., 2014 and CDDEP, 2015). These countries also have high rates of AMR in many common pathogens (Center for Disease Dynamics, Economics and Policy, 2015).

In England, considerable geographical variability in antimicrobial prescribing is evident. The English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR) report (Public Health England, 2015) showed, based on data from one year cross section, that Merseyside had the highest combined general practice and hospital usage of antibiotics from 2010 to 2013. In addition, the highest usage from general practice was in Durham, Darlington and Tees. Findings of this report show that areas of high consumption of antibiotics commonly had higher antibiotic resistance.

1.4.2 Over-the counter use of antibiotics

Antimicrobial self-treatment is another factor that influences AMR. The OTC use of antimicrobials may be inappropriate owing to the uncertainty of diagnosis, or sub-optimal dosing and duration of antimicrobial course (World Health Organization, 2001).

Despite the presence of laws to govern prescribing of antibiotics, they are not enforced in developing countries. Antibiotics may be bought freely without a prescription in many

developing countries. Non-prescription-based use of antibiotics has been reported to range from 19% to over 90% outside the United States and Europe (Morgan et al., 2011). In 2010, 88 to 91% of all antibiotic sales in a sample of rural and urban pharmacies in Vietnam were without a prescription (Nga do et al., 2014). Also, 78% and 87-97% of pharmacies in Saudia Arabia and Syria, respectively, dispensed antibiotics without a prescription (Al-Faham et al., 2011, Bin Abdulhak et al., 2011).

In the UK, all antibiotics require a prescription in order to be dispensed with the exception of some antiviral agents (acyclovir) and antifungals (fluconazole) that can be obtained without a prescription under certain conditions. It has been shown 80% of antibiotic prescribing is for oral formulation in the community (Butler et al., 2007).

1.4.3 Antibiotics use in hospitals and the spread and transmission of resistant bacteria.

Hospitals are the location of treatment for those patients with complex infections caused by resistant pathogens which have been acquired in the community. They are among the areas of clinical practice where AMR has or is likely to have the greatest impact (Department of Health, 1998) (see table 2). Intensive care units (ICUs) and Admission wards are areas within hospitals where patients with severe infections are often located. Excessive prescribing of antimicrobials and the use of invasive devices, such as urinary and/or vascular catheters, and mechanical ventilation contribute to the high resistance rates reported in the ICUs (Department of Health, 1998).

Table 2: Association between antimicrobial resistance and antimicrobial use in hospitals

Changes in antimicrobial use are linked with changes in the prevalence of resistance.
Antimicrobial resistance is less prevalent in community-acquired bacterial infections compared with those from health care-associated infections in hospitals.

Patient with no health care-associated infections are less likely to have received antimicrobials than patients with health care-associated infections caused by resistant strains.

Areas within hospitals that have the highest rates of antimicrobial use tend to have the highest rates of antimicrobial resistance, such as ICUs and Admission wards.

The likelihood of colonisation with resistant pathogens increases with increasing duration of patient exposure to antimicrobials

Adapted from (Shlaes et al., 1997).

The initial emergence of resistant pathogens and their spread are two overlapping consequences commonly seen in hospitals (Department of Health, 1998). Transmission of antimicrobial-resistant pathogens from patient to patient or from hospital professional to patients within the hospital environment are examples of horizontal transmission of infection that exacerbate the problem of AMR (World Health Organization, 2001). In addition, poor hygiene and hand-washing procedures, increased movement of patients within hospitals, and increased transfer of colonised or infected patients from hospitals to other health care settings further exacerbate the situation. Evidence shows that effective infection control practices decrease the spread of resistant pathogens in hospitals and health care facilities. The SENIC study (Haley et al., 1980, Hughes, 1987 and World Health organisation, 2001) showed that effective infection control procedures were successful in reducing rates of nosocomial infections.

1.4.4 Antibiotic prescribing rationale

Antibiotics are prescribed for a range of clinical reasons including therapeutic, prophylactic and empirical treatment of disease. Unnecessary antibiotic prescribing exerts selection pressure and is manifested by inappropriate empirical treatment and inappropriate surgical prophylaxis (Department of Health, 1998).

Empirical antimicrobial therapy should only be prescribed when an infection is suspected and the causative pathogen(s) is/are unknown. Empirical therapy is recommended by prescribers in suspected infections in order to commence treatment promptly. However, it drives AMR and

exacerbate selection pressure by: i) potentially prescribing antimicrobials for non-infectious diseases, ii) potentially initiating unsuitable empirical antimicrobial therapy, and iii) prescribing of broad spectrum antimicrobials to cover all likely pathogens (Yu et al., 1991). Appropriate empirical therapy should be prescribed depending on the most likely pathogens and local susceptibility data. Failure to provide such information to prescribers in a timely fashion is one reason why empirical treatment is sometimes unsuccessful. One US study (Yu et al., 1991) reported that 34% of empirical treatment prescriptions for patients with bacteraemia were irrational and the reasoning behind the choice of antimicrobial agent was suboptimal in 57% of the cases. The use of ciprofloxacin for lower respiratory infections caused by *Streptococcus pneumoniae* and the use of vancomycin for febrile neutropenic patients that could be managed by β -lactams antibiotics are common examples of irrational empirical antimicrobial therapy. Ideal empirical treatment should start with a broad spectrum antimicrobial agent to cover all likely pathogens followed by switching to a narrow spectrum antimicrobial agent that minimises this pressure once the culture and sensitivity results have been obtained. Unfortunately, prescribers often continue with the use of the wide spectrum antimicrobial agent rather than streamlining therapy to a narrow spectrum antimicrobial agent.

Excessive use of antimicrobial prophylaxis for surgical procedures and prolonged peri-operative antimicrobial prescribing are additional reasons which contribute to irrational antimicrobial prescribing in hospitals. Evidence demonstrates that some patients benefit from such prophylaxis while other do not (Leaper, 1998, McDonald et al., 1998, Song and Glenny, 1998, Woods and Dellinger, 1998, Polk and Christmas, 2000). Adding to the problem is the failure to differentiate between infection and inflammation which can lead to prescribing antimicrobials for longer than required (Department of Health, 1998). These prescribing patterns are likely to increase treatment costs and also expose patients to large amounts of antimicrobials leading to high colonisation rates of resistant nosocomial microbes (Aiken et

al., 2012). The choice, dose or duration of pre-surgical antimicrobials may be inappropriate. Published evidence shows that between 19 % and 86 % of patients in hospitals in India may have received inappropriate antibiotic prophylaxis (Belagali et al., 2013, Rana et al., 2013).

Broad spectrum antimicrobials are by definition effective against a wide range of pathogens and continue to be prescribed unnecessarily and inappropriately for potential, unproven infections awaiting culture and sensitivity results. Use of these agents is prolonged in some patients even when a specific pathogen is identified. A US study (Braykov et al., 2014 and CDDEP, 2015) reported that 59 % of patients in six hospitals received appropriate therapy matching cultures, and by the fifth day of therapy, 66 % of antimicrobial therapy regimens were unadjusted, despite negative cultures in 58 % of patients. The study also showed that 30 % of patients did not have clinical signs of infections such as fever or elevated white blood cell count to justify their use. These results demonstrated that the empirical use of broad-spectrum antimicrobial therapy was unnecessary as patients did not have clinical signs of infection, and that treatment was not adjusted or discontinued even when culture and sensitivity data did not show evidence of infection. Another US study (Fridkin et al., 2014 and CDDEP, 2015) showed that half of hospitalized patients in 323 hospitals across the United States received an antimicrobial agent, often broad-spectrum agents. Of which, 37 % of treatments could have been optimised, mainly through better use of diagnostic tests.

1.4.5 Variation in Regimen (Dose and duration)

There is no evidence to rationalise the variations in dose and duration of antimicrobial therapy. Excessively prolonged antimicrobial therapy is likely to increase the selection pressure for resistance in human normal flora. However, excessively short antimicrobial courses are likely to select the least susceptible members of the infective population. For example, brief anti-tubercular therapy owing to poor compliance with standard regimens led to the emergence of multi-drug resistance in *Mycobacterium tuberculosis* (Moore et al., 1997). Sub-therapeutic

dosage (one dose) of antimicrobial therapy for the management of sexually transmitted diseases, such as single dose ceftriaxone for treating *Neisseria gonorrhoea*, is another example of such an issue (World Health Organisation, 2001). *Neisseria gonorrhoea* has become resistant to first-line antibiotics leaving third generation cephalosporins (ceftriaxone or cefixime) the last resort for single treatment. Further complicating the situation is the declining susceptibility of *N. gonorrhoea* to third-generation cephalosporins in different parts of the world mainly low and middle income countries (CDDEP, 2015). Because of concerns about emerging gonococcal resistance, treatment guidelines recommended dual therapy for gonorrhea with a cephalosporin plus either azithromycin or doxycycline. A better approach would be to use combination of antibiotics to have a synergistic effect. Combination of antibiotics may be effective even if the pathogen is resistant to each antibiotic separately. These treatment regimens appear effective and should be considered in all settings. However, the dual antimicrobial regimens, implemented in limited geographic regions, will not entirely prevent resistance emergence and it is only a matter of time when treatment failures with these dual antimicrobial regimens will emerge

1.4.6 Prescribers competency and behaviour

The behaviour of prescribers has been shown to drive the emergence and spread of AMR (World Health Organization, 2001). Therefore, initiatives to improve prescribing patterns and decrease suboptimal use of antimicrobials are essential. The decision to prescribe or not prescribe antimicrobials is multifactorial and dependent on multiple interlinked parameters that differ according to the location, social behaviour of prescribers and the systems used for prescribing medications (World Health Organisation, 2001). Current strategies to optimise antimicrobial prescribing depend on the provision of appropriate information about medications and diseases and the adoption of such knowledge by prescribers in order to influence their practice. However, evidence shows that this approach is rarely adopted and

further research is required to justify the current prescribing behaviour and the barriers to adopt such approach (Wong et al., 2015). A number of causes have been put forward in order to rationalise the suboptimal prescribing patterns shown by prescribers for example: lack of knowledge and training, lack of access to information, perception of patients demands and lack of adherence to guidelines (World Health Organization, 2001).

Lack of knowledge of microbiology and infectious diseases plays a critical role in inappropriate antimicrobial prescribing (Kunin et al., 1987 and World Health organisation, 2001). In addition, the inadequate training of medical students owing to the suboptimal coverage of antimicrobial pharmacology, pharmacokinetics and pharmacodynamics in medical school undergraduate curricula which has resulted in poorly trained prescribers (Tomasz, 1994 and World Health Organisation, 2001). In addition, the format of educational interventions, such as printed materials, to address the lack of knowledge that have not been shown to be effective in changing prescribing behaviour (World Health Organisation, 2001). Several studies in the United States and the European Union showed inappropriate use of antimicrobials in treating patients with viral respiratory infections (Nyquist et al., 1998 and World Health Organisation, 2001). A Chinese study (Hui et al., 1997 and World Health Organisation, 2001) showed that 63% of antimicrobials that were used to treat diagnosed bacterial infections were found to be suboptimal. Gumodoka and co-workers reported that a quarter of patients in their medical districts received parenteral antimicrobials, of which 70% were found to be unnecessary (Gumodoka et al., 1996).

Lack of access to up-to-date information negatively influences antimicrobial prescribing decisions of prescribers (World Health Organisation, 2001). This may result in broad spectrum antimicrobials being excessively prescribed to treat infections that could be treated with narrow spectrum antimicrobials. Also, there is lack of up-to-date treatment guidelines which further exacerbates the problem by increasing the likelihood of prescribing older antimicrobials that

are no longer cost-effective, safe, or effective because of AMR. Clinical guidelines are a core element in supporting clinical practice, however, evidence has shown that their impact is limited when they are not optimally circulated (Grimshaw and Russell, 1993). Factors that increase the adherence to guidelines include the engagement of end-users in the development process, and the presentation of guidelines in simple, easily comprehended format.

Worry that patients may experience bad clinical outcomes pressures prescribers to prescribe antimicrobials excessively especially when the diagnosis is not confirmed. Overprescribing of antimicrobials is also influenced by prescribers' perceptions towards patients' needs and expectations (Macfarlane et al., 1997b, Bosu and Ofori-Adjei, 1997, Butler et al., 1998, World Health Organisation, 2001). One example of overprescribing practices is the excessive prescribing of parenteral antimicrobials when narrow spectrum oral antimicrobials would be more suitable (Gumodoka et al., 1996 and World Health Organisation, 2001).

Qualitative research has shown that patients perceived prescribers who did not prescribe antimicrobials as an imperfect source of care. Consequently, patients may look for other more desirable and informed source of care where physicians would prescribe advanced, expensive broad-spectrum antimicrobial agents more readily (Barden et al., 1998 and World Health Organisation, 2001).

Clinical guidelines are essential in supporting decision making in medical practice (World Health Organisation, 2001). Their development should be local and regional, and involve wide input and the utilisation of information from local surveillance (World Health Organisation, 2001). Evidence shows that antimicrobial prescribing is inconsistent with well-established, evidence-based guidelines (World Health Organization, 2001). Such lack of adherence to antimicrobial prescribing guidelines has a significant effect on the emergence of resistant pathogens and also on the pharmacy expenditure of a hospital if the antimicrobials are

expensive. It has been shown antimicrobials form 30% of a hospital medicine expenditure (John and Fishman, 1997). In an analysis of antimicrobial prescribing in ten studies from teaching hospitals worldwide, 41% to 91% of all antimicrobials prescribed were judged to be irrational choices (Hogerzeil, 1995 and World Health Organisation, 2001). One study (Pestotnik et al., 1996) showed that computerised antimicrobial guidelines led to stabilisation of resistance trends of selected hospital acquired infections over a seven-year period (World Health Organisation, 2001).

1.4.7 Patients and public behaviour

Patient-related factors contribute to the sub-optimal use of antimicrobials and the development and spread of AMR (World Health Organization, 2001). The perception that most infections require treatment with antimicrobials influences patient expectations to receive a prescription of an antimicrobial from their health care professional. Patient-related factors that are believed to influence AMR include: patient misconceptions, self-treatment, and poor compliance with dosage regimens (World Health Organization, 2001).

Many patients believe that infections should be managed by the use antimicrobials regardless of the type of causative pathogen. In a study by Macfarlane, most patients questioned that their respiratory symptoms were due to infections and the use of an antimicrobial was crucial (Macfarlane et al., 1997 and World Health Organisation, 2001). This increases the financial burden on health care systems and further increases the selection pressure of resistance for newer antimicrobials. Many patients misunderstand the principle of AMR which makes antimicrobials a unique class of drugs amongst other medications (World Health Organization, 2001).

Mounting evidence shows that lack of patients' understanding and poor communication with health care providers are the main reasons for patients being not compliant with their medication regimens (Buckalew and Sallis, 1986). Some patients fail to receive a full course

of antimicrobials because of their high price which leads to early cessation of therapy. Other patients believe that an antimicrobial course can be stopped once they feel better which further exacerbates AMR and leads to treatment failure.

1.4.8 Use of antimicrobials in agriculture and animal food production

Antimicrobials have been used to prevent and treat infections in animals and to promote their growth (Center for Disease Dynamics, Economics & Policy, 2015). It has been estimated that more antimicrobials are used in animals than in the human population. In the United States, more than 80% of all antibiotics are used in food animals (US Food and Drug Administration, 2010). The increase in use of antibiotics in animal food production is driven by the growing human population, from 7 billion today to an estimated 9-10 billion by 2050 (Center for Disease Dynamics, Economics & Policy, 2015). Demand for animal protein (meat) and other animal products is anticipated to approximately double by 2050 (Center for Disease Dynamics, Economics & Policy, 2015). According to the United Nations Food and Agriculture Organization (FAO), it is anticipated that meat consumption will increase by 73%, and dairy products consumption by 58 % over 2011 levels (Food and Agriculture Organization, 2011).

Antimicrobials are used to prevent and treat infections in both humans and animals. In humans, antimicrobials may be used prophylactically, before major surgery or to prevent surgical site infection, and therapeutically to treat confirmed infections. In animals, antimicrobials, however, may be given to an entire group to prevent epidemic spread of infections in the entire population (Center for Disease Dynamics, Economics & Policy, 2015). The main purpose of using antimicrobials in animals is to promote growth. It has been shown that the antimicrobials used in animals are similar to those used in humans. The most commonly used antimicrobial classes by global sale for animals in 2009 were penicillins (\$600 million), macrolides (\$600 million), and tetracyclines (\$500 million) (Center for Disease Dynamics, Economics & Policy, 2015). It has been estimated that global consumption of antimicrobials in animals was 63,200

tons in 2010 and by 2030, this figure is estimated to increase to 105,600 tons (Center for Disease Dynamics, Economics & Policy, 2015).

Evidence connects antimicrobial use in animals with effects on humans demonstrated by: i) the direct animal-to-human transmission of resistance, ii) animal food-to-human transmission of resistance, iii) and food-borne outbreaks of infection (Center for Disease Dynamics, Economics & Policy, 2015). Antibiotic resistant bacteria may be transmitted from animals to their human carers. Identical strains of antibiotic-resistant bacteria have been isolated in animals and their human handlers (Zhang et al., 2009). Antibiotic-resistant bacteria may be passed from animal food to humans. Resistant strains of *E. coli* and MRSA have been found in animal products such as beef (Marshall and Levy, 2011). These strains can be transmitted to people who handle these foods before cooking or after inappropriate cooking. Large outbreaks of food-related infections have occurred around the world such as a major *Salmonella* outbreak in 1985 in the United States (Center for Disease Dynamics, Economics & Policy, 2015). This outbreak resulted in one death and was linked to unpasteurized milk (Tacket et al., 1985 and CDDEP, 2015). The nalidixic acid-resistant *Salmonella* outbreak, which occurred in 1998 in Denmark, was connected to pork use, and the identical resistance factor was found in human patients and herds (Molbak et al., 1999 and CDDEP, 2015).

1.5 The health and economic burden owing to antimicrobial resistance

Since the introduction of antimicrobials, the economic and safety burden of AMR has steadily accelerated nationally and internationally (Hawkey, 2008). The health and economic burden of AMR is multi-factorial demonstrated by the increasing morbidity and mortality rates and the increased length of stay owing to inadequate or unsuccessful treatment of patients with infections, coupled with the loss of the first-line antimicrobials and the need to use more expensive, last resort antimicrobials (Hawkey, 2008).

In 2014, research work led by the UK government appointed a UK economist to evaluate the future burden and cost of AMR showed that a sustained increase in AMR would result in a global death rate of 10 million people every year and a reduction of 2% to 3.5% in gross domestic product (GDP) by 2050 (O'Neill, 2014). It is estimated that the world will incur a cost of 100 trillion USD as a consequence of AMR (O'Neill, 2014).

According to the U.S. Centres for Disease Control and Prevention (CDC), more than 2 million infections and 23,000 deaths each year in the United States are attributable to antibiotic resistance at a direct cost of \$20 billion and additional productivity losses of \$35 billion (Centres for Disease Control and Prevention, 2013). In the United States, an estimated medical cost of \$18,500–29,000 per patient, and an estimated extra length of hospital stay of 6.4–12.7 days were attributable to AMR infections in 2009 (Duguid and Cruickshank, 2011). A report to the US congress in 1995, the estimated the annual extra cost for treating health care acquired infections (HCAIs) caused by six types of resistant bacteria was at least \$ 1.87 billion (U.S. Congress, Office of Technology Assessment, 1995).

In Europe, the ECDC/EMA Joint Technical Report (European Centre for Disease Prevention and Control/European Medicines Agencies, 2009) estimated that antibiotic resistance is responsible for 25,000 deaths, costing €1.5 billion annually in direct and indirect costs. The report also estimated that the annual productivity losses owing to absence from work of infected patients or due to death of infected patients were about €150 million, € 450 million, respectively.

In the UK, the ECDC/EMA Joint Technical Report estimated, by extrapolating data related to the UK from this report, that multi-drug resistant (MDR) bacteria were responsible for 3,000 deaths annually (European Centre for Disease Prevention and Control/European Medicines Agencies, 2009).

A WHO report (World Health Organization, 2014), found there was a significant increase in all-cause mortality and 30-day mortality for patients with third-generation cephalosporin and fluoroquinolone-resistant *E. coli* infections; third-generation cephalosporin and carbapenem-resistant *K. pneumoniae* infections and methicillin-resistant *S. aureus* infections (MRSA). Additionally, the report showed no significant increase in total length of stay for patients with the above-mentioned resistant bacteria strains except for MRSA.

The report identified few studies (Cosgrove et al., 2003, Smith and Coast, 2013) with economic evaluations which demonstrate that the costs for treating resistant infections were higher than that for treating non-resistant infections. Additionally, the percentage of patients with cephalosporin or fluoroquinolone-resistant *E. coli* infections requiring admission to the intensive care unit was shown to be higher compared to that for patients with non-resistant infections. One study (Alam et al., 2009) from the United Kingdom reported that treating urinary tract infections caused by resistant *E. coli* treated in primary care had an additional cost of £3.62 per patient.

1.6 Surveillance systems

AMR is a major problem to the public health in the UK and across the globe. Antimicrobial agents are essential for the management of common community and health-care acquired infections. Clinical decisions of the choice of empirical treatment demand knowledge of the likely causative pathogen(s) and the susceptibility profile to antimicrobial agents. Surveillance systems provide a platform for understanding both the changing patterns and trends of epidemiology of infections and AMR and the changing patterns of susceptibility of the causative pathogens over time. This will inform decision making and interventions, specifically treatment guidelines, aimed at reducing the health and economic burden of AMR and will establish the basis for evaluating the effectiveness of such interventions.

Surveillance systems have been established in the UK and internationally. The WHO implemented initiatives to monitor AMR and raise awareness to its clinical and economic burden. In 2014, WHO in collaboration with Member States and other partners produced a report (World Health Organization, 2014) entitled ‘Antimicrobial Resistance: Global Report on Surveillance’. This report provides the most recent overview of the extent of AMR and the current state of surveillance globally. EARS-Net is a European surveillance system which provides estimates of AMR patterns for European countries and is funded by the European Center for Disease Prevention and Control (ECDC). Public Health England (PHE) established the English Surveillance Programme on Antimicrobial Use and Resistance (ESPAUR) in response to the UK strategic plan for controlling AMR. This report provides an overview of antibiotic resistance and consumption in England from 2010 to 2014. Detail of findings of these reports are discussed in the next section.

1.7 Patterns and trends of antibiotic resistance

The current section provides an overview of the best available data on antibiotic resistance patterns in England and worldwide. For international antibiotic resistance rates, data was obtained from a global database known as ResistanceMap developed by WHO, the Center for Disease Dynamics, Economics and Policy (CDDEP) and scientific publications (World Health Organisation, 2014). ResistanceMap is an interactive tool that provides information of the current antibiotic resistance rates of selected pathogens in the United States, Europe and low- and middle-income countries. For England’s antibiotic resistance detail, the English Surveillance Programme of Antibiotic Utilisation and Resistance (ESPAUR) was used to get information on AMR.

1.7.1 Global patterns and trends of antibiotic resistance

According to WHO, *Staphylococcus aureus*, *Escherichia coli* and *Klebsiella pneumonia* are listed among the top three species of bacteria of greatest concern causing infections in the

community and in hospital settings. The incidence of methicillin resistant *Staphylococcus aureus* (MRSA) has decreased in Europe and the United States over the last 8 years to 18% and 44%, respectively (EARS-Net, 2014, CDDEP, 2015). Also, it has started to decrease in South Africa to 28% because of antimicrobial stewardship initiatives (Kariuki and Dougan, 2014). The incidence of methicillin resistant *Staphylococcus aureus* is still increasing in other parts of the world including India, Australia and Latin America (CDDEP, 2015).

The virulence of *E. coli* isolates has increased owing to its ability to produce extended-spectrum beta-lactamases (ESBLs). ESBLs are enzymes produced by Gram-negative bacteria that have the capacity to deactivate penicillins, cephalosporins and monobactams (WHO, 2014). In 2013, it was shown that the percentage of *E. coli* isolates producing ESBLs was 85% in 17 of 22 European countries (EARS-Net, 2014). In 2009 and 2010, the percentage of *E. coli* isolates producing ESBLs was 28% in 11 countries in Asia and, their resistance rates to third and fourth-generation cephalosporins ranged from 26% to 50% (Lu et al, 2012).

Carbapenems are losing their effectiveness against Enterobacteriaceae. In 2013, five European countries reported increases in prevalence of carbapenem-resistant Enterobacteriaceae (CRE) (EARS-Net, 2014). In 2012, 11% of *K. pneumonia* and 2% of *E. coli* in US hospitals were resistant to carbapenems (CDC, 2013). In India, resistance rates of *E. coli* in 2013 and *K. pneumonia* in 2014 to carbapenems were 13% and 57%, respectively (CDDEP, 2015). *E. coli* and *K. pneumonia* isolates carrying an ESBL known as New Delhi metallo-beta-lactamase 1 (NDM-1) accounts for the majority of carbapenem resistance in many countries (Pillai et al., 2011). NDM-1 contains resistant genes that can be transferred between Gram negative bacteria. NDM-1 is resistant to the majority of antibiotics except polymyxins (Moellering, 2010).

There are other emerging resistant pathogens of concern including *Clostridium difficile*. It has been shown that the risk of *C. difficile* infections is increased by antibiotic use by 7-10 fold for

up to one month after therapy discontinuation (CDDEP, 2015). It has been estimated that the incidence of *Clostridium difficile* could decrease by 26% if the use of broad spectrum antibiotics in hospitalised patients was reduced by 30% (Fridkin et al., 2014) In the United States, it is responsible for more than 14,000 deaths and 250,000 infections annually (CDC, 2013).

Vancomycin-resistant enterococci are another class of bacteria of concern that fuels the problem of resistance. Since their first discovery in 1987 in Europe within a decade, they were found to be the causative agent in 25% of enterococcal bacteraemias in hospitals in the United States (Willems et al, 2005 and CDDEP, 2015). By 2013, vancomycin had lost its effectiveness against 77% of *E. faecium* healthcare-associated infections in the United States (CDC, 2013 and CDDEP, 2015).

A particularly resistant strain of *Salmonella typhi*, H58, has shown multidrug resistance (CDDEP, 2015). It has originated in different parts of Asia and Africa and has spread throughout these regions. In 2011, the first resistant strain was detected in Malawi and its prevalence had increased from 7% of cases in 2010 to 97% of cases in 2014 (Feasey et al, 2015 and CDDEP, 2015).

1.7.2 UK patterns and trend of AMR

This section addresses antibiotic resistance of selected pathogens and on antibiotic consumption in England. Data were derived from the English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR)(Public Health England, 2014).

There was an increase in the incidence of *E. coli* and *K. pneumonia* bloodstream infections from 2010 to 2014 of 15.6% and 20.8%, respectively (Public Health England, 2015). There was no change in the incidence of *K. oxytoca*, *Pseudomonas* spp., *Enterococcus* spp., *S. aureus* and *Acinetobacter* spp. bloodstream infections over the same period (Public Health England, 2014). There was a decline in the incidence of *Streptococcus pneumonia* bacteraemias. The

overall incidence of *S. pneumonia* bacteraemias in England declined by 25% from 2010 to 2013 (Public Health England, 2014). Resistance in tuberculosis and gonorrhoea have stabilised though there were reports of azithromycin resistance in heterosexuals in the northern part of England in 2014. The percentage of enterococci isolates from blood and other sites resistant to vancomycin were 14.4% and 8.1%, respectively. There is a year-on-year increment in the number of carbapenem-resistant isolates from different sources including blood, urine, faeces (Public Health England, 2014).

Table 3: Reports of the percentages of antibiotics resistant isolates in cases of tuberculosis, gonorrhoea and bloodstream infections in 2010 and 2014

Bacteria	Antibiotic class	Percentage resistance	of 2014 compared to 2010
Bloodstream infections			
<i>Escherichia coli</i>	Ciprofloxacin	18.7	↔
	Cefotaxime and/or ceftazidime	11.1	↑
	Gentamicin	9.6	↔
	Imipenem or meropenem	0.1	↔
	Co-amoxiclav	42.0	↑
	Piperacillin/tazobactam	11.0	↑
<i>Klebsiella pneumonia</i>	Ciprofloxacin	10.9	↔
	Cefotaxime	12.1	↑
	Gentamicin	7.5	↔
	Imipenem and/or meropenem	1.5	↑
<i>Pseudomonas spp.</i>	ceftazidime	7.4	↔
	Imipenem and/or meropenem	11.5	↔
<i>Streptococcus pneumonia</i>	Penicillin	4.2	↔
<i>Enterococcus spp.</i>	Vancomycin	14.2	↑
<i>Staphylococcus aureus</i>	Methicillin	10.0	↓

Bacteria	Antibiotic class	Percentage resistance	of 2014 compared to 2010
<i>Acinetobacter</i> spp.	Colistin	3.5	↔
Gonorrhoea			
<i>Neisseria gonorrhoeae</i>	Ceftriaxone	0.0	↔
	Azithromycin	1.0	↔
Tuberculosis			
<i>Mycobacterium tuberculosis</i>	Isoniazid	6.9	↔
	Rifampicin and isoniazid	1.3	↔

Adapted from Public Health England: ESPAUR 2015; the arrows means the following: ↑ statistically significant increase; ↓ statistically significant decrease; ↔ no statistically significant change

1.8 Pattern and trends of antibiotic consumption

For global antibiotic consumption, the IMS MIDAS (a database that estimates the use of antibiotics consumption from the volume of antibiotics sold in retail and hospital pharmacies) was used to obtain data related to antibiotic consumption (CDDEP, 2015).

It is essential to understand how antibiotic use is reported and what the sources of reporting are for antibiotic use. Data on antibiotic consumption is of great value to those involved in healthcare management and policy-makers in designing interventions and policies aimed at optimising the use of antibiotics, curtailing AMR, benchmarking comparisons and assessing the outcomes of antimicrobial stewardship interventions (Public Health England, 2014).

There are metrics to measure the volume of antibiotic usage which reflect an aggregate or average amount of antibiotic being used at the level of the patient, unit, entire institution or at the national level (Ibrahim and Polk, 2014). Aggregate antibiotic use is usually expressed as a ratio of numerator and denominator. The most commonly used metric for measuring antibiotic consumption are Defined Daily Doses (DDD) (WHO, 2012). Days of therapy (DOT) and length of therapy (LOT) are other metrics used more commonly in the United States (Ibrahim and Polk, 2014). The numerator is divided by a denominator which can be bed days or number

of admissions and is often normalised to 100 or 1000 patients. The bed days measure is the product of the number hospital beds occupied and the mean length of stay. Table 4 shows the most commonly used metrics to measure antibiotic consumption (Ibrahim and Polk, 2014).

Table 4: Summary of measurement units commonly used to report antibiotics consumption with advantages and disadvantages.

Measurement unit	Advantages	Disadvantages
Defined Daily Dose (DDD)/1000 bed-days	<ul style="list-style-type: none"> • <i>Easily calculated</i> • <i>Standardised comparisons of antimicrobial use between hospitals and countries.</i> • <i>Doesn't require patient level data</i> 	<ul style="list-style-type: none"> • <i>'Overestimate or underestimate Days of Therapy (DOT)</i> • <i>Not applicable to paediatrics</i>
Days of therapy (DOT)/1000 bed-days	<ul style="list-style-type: none"> • <i>DOT is not affected by changes in WHO reference DDDs</i> • <i>Measure paediatric use</i> • <i>Bed days incorporates length of stay in the antimicrobial use measure.</i> 	<ul style="list-style-type: none"> • <i>DOT doesn't measure dosage</i> • <i>May underestimate exposure in renal impairment</i> • <i>Doesn't underestimate the duration of therapy</i> • <i>Require patient level data</i> • <i>Bed days inflates apparent use if length of stay declines over time</i>
Days of therapy (DOT)/1000 admissions	<ul style="list-style-type: none"> • <i>Admission in the denominator</i> • <i>Not a function of length of stay</i> • <i>May correlate better than bed-days</i> 	<ul style="list-style-type: none"> • <i>Admissions in the denominator</i> • <i>Doesn't consider length of stay; must be adjusted before used for benchmarking</i> • <i>An uncommon metric for most hospitals</i>
Length of Therapy (LOT)/discharge or admission	<ul style="list-style-type: none"> • <i>Provide an aggregate-level estimate of the average duration of therapy among patients who received antibiotics</i> • <i>Dose-dependent (can be used in paediatrics)</i> 	<ul style="list-style-type: none"> • <i>Not normalised for length of stay, should be risk adjusted for SOI or case mix before used for benchmarking</i> • <i>Unlike DOT, LOT cannot be used to compare use of specific drugs</i> • <i>Patient level data are needed for its calculations</i>

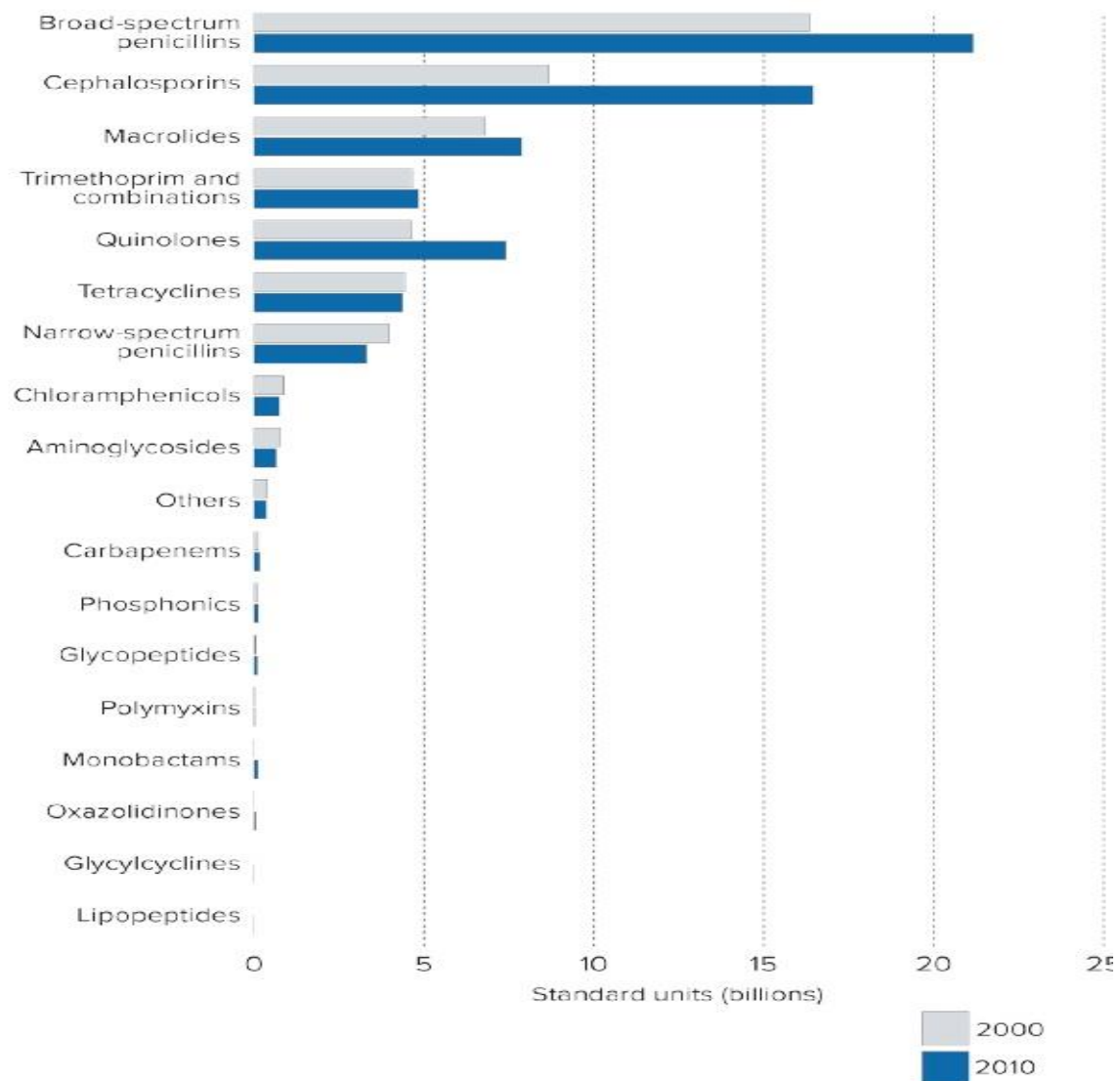
Measurement unit	Advantages	Disadvantages
Length of stay/1000 bed-days	<ul style="list-style-type: none"> • <i>Can be calculated for all admissions in a unit or service line providing a measure of the intensity of antimicrobial use</i> • <i>Normalized for length of stay making possibly useful for benchmarking purposes</i> 	<ul style="list-style-type: none"> • <i>A proportion that does not estimate the duration of therapy</i> • <i>Patient level data are needed for its calculation</i>
Days of therapy/Length of stay ratio	<ul style="list-style-type: none"> • <i>Provides measure for combination therapy at the aggregate level</i> 	<ul style="list-style-type: none"> • <i>Doesn't measure the proportion of patients who receive combination therapy</i> • <i>Patient level data are needed for its calculation</i>
Proportion of patients receiving antimicrobial therapy	<ul style="list-style-type: none"> • <i>Provide another dimension of antimicrobial use that can be targeted by antimicrobial stewardship programmes</i> 	<ul style="list-style-type: none"> • <i>Risk adjustment must ensure that groups being compared are similar in number and severity of infections</i>

Adapted from (Ibrahim and polk, 2014)

1.8.1 Global patterns and trends of antibiotic consumption

New estimates of global antibiotic consumption have been released to estimate the volume of antibiotic used in hospital and retail pharmacies for 71 countries from 2010 to 2014 (Van Boeckel et al, 2014 and CDDEP, 2015). There was an increase in the total global antibiotic consumption by 30% from 2000 to 2010. The global consumption grew from 50 billion to 70 billion standard units² (SU). The most frequently consumed antibiotics were penicillin and cephalosporins; recorded 60% of total consumption in 2010 (see figure 1).

Figure 1 Global antibiotic use by class, 2000-2010



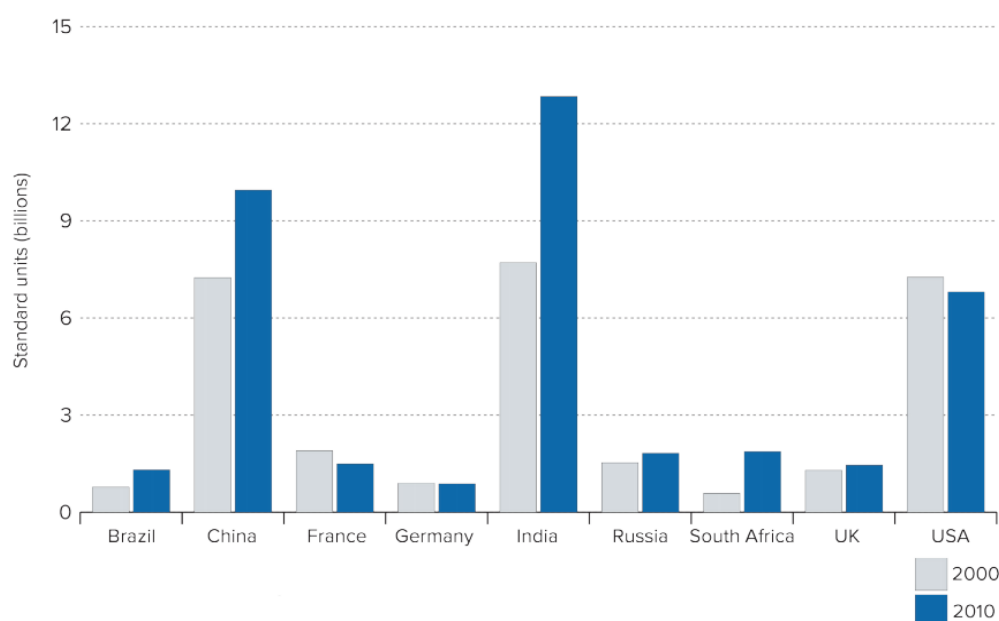
Adapted from Van Boeckel et al. 2014 and CDDEP, 2015

There is no single standard measure that enables the detailed understanding of prescribing. The defined daily dose (DDD) is the only unit of measurement that can be combined across all settings. The DDD is ‘the assumed average maintenance dose per day for a medicine used for its main indication in adults’ (WHO, 2012).

Evidence from around the world shows significant increases for last-resort antibiotics between 2005 and 2010 including carbapenems (approximately 40%) and polymyxins (13%) (Van Boeckel et al, 2014). In Europe, carbapenems consumption has also increased and it was measured in defined daily doses (DDD) per 1,000 inhabitants per day (DID). In 1997, consumption ranged from 0.0014 in Slovenia to 0.029 in Belgium. In 2013, it ranged from 0.0136 DID in Bulgaria to 0.381 DID in the UK (ESAC-Net 2015).

The top three countries that consume the most antibiotics in 2010 were India, 13 billion SU; China, 10 billion SU; and the United States, 7 billion SU. However, the United States led in 2010 in per capita terms among these countries with 22 SU per person, in comparison with 11 SU in India and 7 SU in China (Van Boeckel et al., 2014). Antibiotic consumption in high-income countries was maintained or decreased from 2000 to 2010 (figure 1-5). The top five that had the greatest increase in antibiotic consumption from 2000 to 2010 were Brazil (19%), Russia (19%), India (66%), China (37%), and South Africa (219%) (Figure 2)

Figure 2 Total antibiotic consumption in selected countries, 2000 and 2010 (Van Boeckel et al., 2014 and CDDEP, 2015)



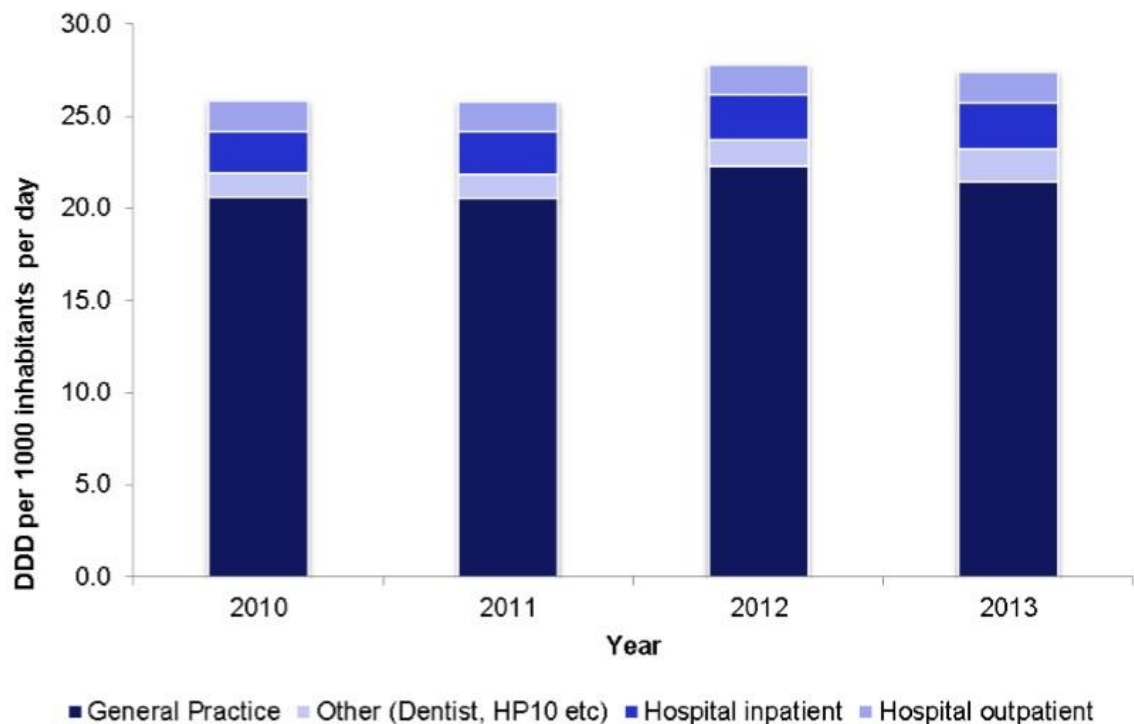
1.8.2 UK patterns and trends of antibiotic consumption

In the UK, about 50% of antimicrobial agents are used in human and about 50% in veterinary medicine or for animal food production (Department of Health, 1998). In 2014, most of antibiotics in England were prescribed in general practice (78.5%), followed by hospital inpatients (9.1%), hospital outpatients (6.2%), and other community settings (6.2%) (Predominantly dentists) (Public Health England, 2014).

There was a significant increase of total antibiotic consumption in primary and secondary care by 6% over between 2010 and 2013; from 25.9 DDD per 1000 inhabitants in 2010 to 27.4 DDD per 1000 inhabitants in 2013 (See figure 3) (Public Health England, 2014). Total antibiotic consumption declined significantly between 2014 and 2015 by 4.3%, from 22.9 to 21.8 DDD per 1000 inhabitants per day. Between 2011 and 2014, there was a significant increase in

prescribing to hospital inpatients by 11.7% and to hospital outpatients by 8.5% (Public Health England, 2014).

Figure 3: Total antibiotic consumption, expressed as DDD per 1000 inhabitants per day, England, 2010-2013 adapted from Public Health England, 2014



The three most commonly prescribed antibiotic classes in England in 2013 were penicillins (75%), macrolides (8.2%) and tetracyclines (3.9%) (Public Health England, 2014). Between 2010 and 2014, there was a significant increase in the use of tetracycline (13%), sulphonamide/trimethoprim (5%), and a mixed group of other antibacterials (23%). This was coincided with a decrease of some antibiotic groups including other β -lactam antibacterials (17%), and antibiotics used to treat *Clostridium difficile* antibiotics (-3%), and quinolones (2%) (Public Health England, 2014).

Between 2010 and 2014, the use of broad spectrum antibiotics within hospitals increased particularly for carbapenems and piperacillin-tazobactam by 36% and 55%, respectively (Public Health England, 2015). Between 2013 and 2014, the rate of increase of these antibiotics

had declined to 4% for carbapenems and 7% for piperacillin/tazobactam (Public Health England, 2015).

Figure 4: Total antibiotic consumption by key antibiotic group, expressed as DDD per 1000 inhabitants per day, across England, 2010-2013 adapted from Public Health England, 2014

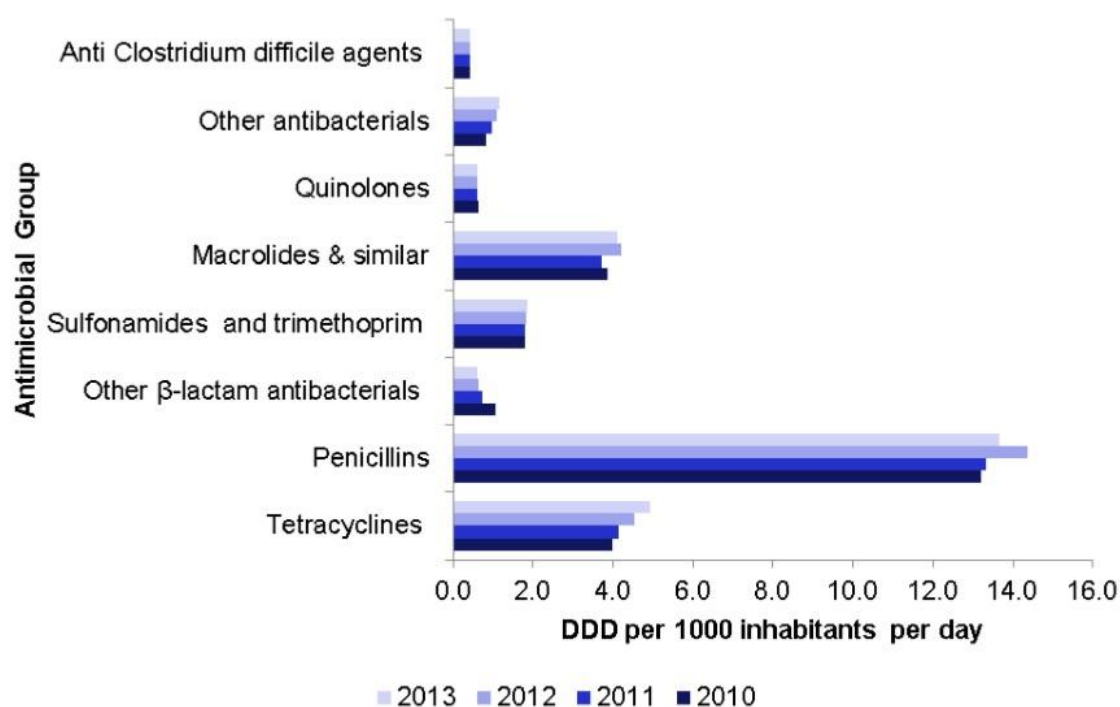


Table 5: Summary of antibiotic consumption in general practice and NHS Trusts, presented as DDD per 1000 inhabitants per day (with changes compared to 2010), England, 2010-2014

	General practice	Compared to 2010	NHS trusts	Compared to 2010
Broad Spectrum Antibiotics				
Penicillin and enzyme inhibitor	0.9	↑	0.9	↑
Cephalosporins	0.26	↔	0.22	↑
Carbapenems	0.001	↔	0.08	↑
Quinolones	0.3	↓	0.2	↔
Narrow Spectrum Antibiotics				
Penicillins (without enzyme inhibitors)	6.2	↑	1.2	↔
Tetracycline	4.5	↑	0.33	↓
Macrolides	2.7	↑	0.5	↑

	General practice	Compared to 2010	NHS trusts	Compared to 2010
Sulfonamides and trimethoprim	1.2	↔	0.4	↑
Proportion of broad spectrum antibiotics/ total antibiotics	8.5%	↓	33.3%	↑
Total antibiotic use expressed as DDD per 1000 inhabitants per day	17.1	↑	4.2	↑
Total antibiotic prescriptions expressed as items per STARPU	1.233	↔		NA

Adapted from Public Health England, 2014

1.9 Policy strategies and guidance to contain AMR

The global nature of AMR requires a global response across countries and multiple sectors. The burden of AMR on the practice of modern medicine has influenced governments to take initiatives to contain the problem. The world is on the verge of a post-antibiotic-era where antimicrobial agents may become ineffective in the management of common infections putting patients at risk. Determining the extent of the problem is paramount for informing the development of effective policy strategies to contain AMR.

1.9.1 Global policy strategies

Many organisations from around the world have designed and implemented effective policy strategies to minimize the emergence and spread of AMR. WHO has taken initiatives to contain AMR, monitor its prevalence and highlight its health and economic burden. In 2001, WHO published a global containment strategy (World Health Organization, 2001), and the focus of World Health Day in 2011 was on AMR (World Health Organization, 2011). The WHO global containment strategy includes proposals to minimise the burden and spread of AMR, facilitate access to appropriate antimicrobial agents, optimise the use of antimicrobial agents, reinforce health systems and their surveillance capacity, strengthen regulations and legislation and support the development of new antimicrobial agents and vaccines. The strategy includes a set

of recommendations directed towards the public, prescribers, hospitals, governments and health systems, animal food production and agriculture industry and pharmaceutical industry.

The strategy also includes interventions directed towards both hospitals and prescribers. Specific advice is given for hospitals which highlights the need for establishing infection control programmes and hospital therapeutic committees, developing antimicrobial prescribing guidelines and formularies, monitoring volume of antimicrobial use and adopting cutting-edge diagnostic laboratories. They may inform decision making and optimise the appropriate and cost-effective prescribing of antimicrobial agents. This is a key area in the recommendations for both hospitals and prescribers. To further this recommendation, examining the impact of computerised prescribing guideline systems on adherence to evidence-based antimicrobial guidelines, optimising the prudent use of antimicrobial agents and AMR is fundamental. A study (Pestotnik et al., 1996) showed that computerised antimicrobial guidelines led to stabilisation of resistance trends of selected hospital acquired infections over a seven-year period.

The Alliance of Prudent Use of Antibiotics (APUA) produced a report (Alliance for the Prudent Use of Antibiotics, 2001) that contained a number of key recommendations including raising awareness of antibiotic resistance, strengthening surveillance of antibiotic resistance, promoting the rationale use of antibiotics in both humans and animals, incentivising new antibiotic development, allocating resources to contain antibiotic resistance in poor countries and allocating sufficient fund for surveillance, research and education.

To optimise the use of antibiotics in humans a series of recommendations were made in the APUA reports which were directed to hospitals. It was recommended that each hospital should establish evidence-based guidelines for appropriate antibiotic use and that they are updated based on surveillance data. These guidelines should be relevant to the clinical and

microbiological aspects of a given population and disseminated not only as printed materials, but also via interactive strategies such as the utilisation of HIT including CDSS and eRx.

In 2004, the World Health Organization produced a report (World Health Organization, 2004) aimed at determining priority medicines for Europe and the rest of the World. The report stated that treating infections caused by resistant bacteria was the number one priority given the potential public health consequences if effective new antibacterial agents were not developed.

AMR was the focus of the World Health Day 2011 given the burden of resistance of microbes that cause common and life-threatening infections to antimicrobial agents. This is caused by the excessive and irrational use of antimicrobial agents. In response to that, the WHO launched a policy package (World Health Organization, 2011) which encompasses recommendations committing to countries having a national plan, surveillance, accessibility to antimicrobial agents, the rationale use of antimicrobial agents, infection control and development of new antimicrobial agents

The US Centers for Disease Control and Prevention (CDC) launched a campaign in 2002 (Centres for Disease Control and Prevention, 2002) to contain AMR in hospitals as data showed that each year 2 million patients acquired nosocomial infections during their hospital stay which resulted in ninety thousand deaths. The campaign supported the use of CDSS to improve the quality of antibiotic prescribing and detailed twelve steps which focus on the prevention of infection, diagnosis and effective treatment, using antimicrobial agents rationally and the prevention of infection transmission. The campaign acknowledged the success of CDSS at the LDS hospital, Salt Lake City, Utah.

Recognising the growing burden of AMR, in 2009 the US president Barack Obama and Prime Minister Fredrik Reinfeldt from Sweden created a transatlantic taskforce on antimicrobial resistance (TATFAR, 2014) in 2009. A series of recommendations on AMR were proposed in

order to establish collaboration between the US and Sweden which encompassed many areas including appropriateness of antimicrobial use, infection prevention and control and development of new antimicrobial agents.

The Center for Disease Dynamics, Economics and Policy (CDDEP) issued a report that records that status of World's antibiotics in 2015. This report provided a comprehensive overview of the global trends in antibiotic resistance and antibiotic use, the current antibiotic supply and the development of new antibiotics, and interventions that have been shown to support ensure the rationale use of antibiotics. The report provided a comprehensive policy response encompassing six strategies directed towards reducing antibiotic demand, improving infection control and antimicrobial stewardship, incentivising the appropriate use of antimicrobial agents, reducing use in agriculture and animal food production, improving education and ensuring international political collaboration (CDDEP, 2015).

1.9.2 European policy strategies

In 2001, the European Commission launched a strategy (Commission of the European Communities, 2001a) which encompassed proposals in the areas of surveillance, infection prevention, international cooperation and development of new antibacterial agents. At that time, European Union (EU) Health Ministers also adopted a council strategy (Commission of the European Communities, 2001b) which promoted developing guidelines to optimise the rationale use of antimicrobial agents in humans. Despite the availability of AMR containment strategies such as resistance surveillance, infection control measures and interventions to prevent the development and spread of infections, patients still present with infections caused by multi-drug resistant bacteria that are resistant to many of the existing treatments.

In 2007, the European Medicines Agency (EMA), the European Center for Disease Prevention and Control (ECDC) and the international network Action on Antibiotic Resistance (ReAct) met together to highlight the gap between infections caused by multi-drug resistant

bacteria and the need to develop new antibacterial agents to manage them. To address this gap, an ECDC/EMA Joint Working Group was established in 2008 to produce a report (European Centre for Disease Prevention and Control/European Medicines Agencies, 2009) that provided estimated predictions on the likely availability of new antibacterial agents that would be effective in treating multi-drug resistant bacteria in the coming years. It was shown that fifteen antibacterial agents with new mechanisms of action were in the early phases of development and were being developed to treat bacterial infections for which existing treatments were already available. The report highlighted an increasing trend of resistance to both Gram-negative and Gram-positive bacteria. Additionally, infections caused by multi-drug resistant bacteria were found to be associated with excess mortality, morbidity and cost. The report concluded that there was a lack of truly novel antibacterial agents with new mechanisms of action being developed and there is a lack of antibacterial agents effective against multi-drug resistant Gram-negative bacteria.

1.9.3 UK policy strategies

In 2015, the NHS England, Public Health England, and Health Education England produced a joint National Patient Safety Alert to underscore the seriousness of AMR and the need for policies to contain AMR and optimise the use of antibiotics. The Prime Minister in July 2014 stated that action should be taken to avoid a post-antibiotic era and to preserve the efficacy of the antibiotics in use (Public Health England, 2015).

Concern regarding the magnitude of AMR in the UK has led to the production of a series of government and non-government reports, strategies and actions in recent years as summarized in table 6.

Table 6: UK government and non-government policy reports

Report	Year	Agency
The Path of Least Resistance	1998	Medical Advisory Committee
Resistance to Antibiotics and Other Antimicrobial Agents	1998	House of Lords Select Committee on Science and Technology
UK Antimicrobial Resistance Strategy and Action Plan	2000	Department of Health
Winning ways: Working together to reduce Healthcare Associated Infection in England	2003	Department of Health
Hospital Pharmacy Initiative for Promoting Prudent Use of Antibiotics in Hospitals	2003	Department of Health
The Health Act 2006	2006	Department of Health
Saving Lives: Reducing Infection, Delivering Clean and Safe Care	2007	Department of Health
Antimicrobial Framework	2007	Specialist Advisory Committee on Antimicrobial Resistance (SACAR)
Health and Social Care Act 2008	2008	Department of Health
Clostridium difficile infection: How to deal with the problem	2009	Department of Health and Health Protection Agency
TARGET toolkit	2009	Antimicrobial Stewardship in Primary Care
Annual Report of the Chief Medical Officer: Infection and the rise of antimicrobial resistance	2011	Chief Medical Officer
Start Smart then Focus	2012	Advisory Committee on Antimicrobial resistance and Health Care
UK Five Year Antimicrobial Resistance Strategy 2013 to 2018	2013	Department of Health and Department for Environment, Food and Rural Affairs
English Surveillance Programme for Antimicrobial Utilization and Resistance 2010 to 2014	2015	Public Health England

Adapted from (Dixon and Duncan, 2014) and (Ashiru-Oredope et al., 2012)

In 1998, a report was published by the House of Lords Select Committee on Science and Technology (Parliament. House of Lords, 1998) highlighting the main findings of a sub-committee formed to address issues related to AMR and use of antimicrobials in the United Kingdom. The report stressed the importance of raising awareness and wide spread recognition of AMR, having drug formularies within hospitals, and the way antimicrobials should be prescribed by newly qualified doctors. The report proposed several strategies to contain antimicrobial resistance and optimise antimicrobial prescribing in secondary care. It concluded that there was a paucity of data on antimicrobial use in hospitals and that hospital should adopt and deploy computerised aids to optimise antimicrobial prescribing.

In 1998, the Standing Medical Advisory Committee (SMAC) produced a report (Department of Health, 1998) to examine the problem of AMR in relation to clinical prescribing practice. The report encompassed recommendations related to antimicrobial prescribing in the community and hospitals, prescribing guidelines, education, surveillance, infection control, veterinary and agricultural use and proposals to develop CDSS to aid prescribers make evidence-based decisions. The report stressed the need to promote better prescribing of antimicrobial agents by developing standardized national evidence-based guidelines and integrate them with well-established CDSS.

Following this, the Department of Health produced several reports between 2000 and 2013 on AMR and antibiotic prescribing as summarized in table 3. The first UK Department of Health report ‘Antimicrobial Resistance Strategy and Action Plan’ was produced in 2000 (Department of Health, 2002). The Royal College of General Practitioners (RCGP) and the Antimicrobial Stewardship in Primary Care (ASIP) collaboration, established in 2009, developed the TARGET toolkit designed to influence prescribers’ and the public’s attitudes, perceptions and barriers to optimal antibiotic prescribing and to support general practitioners in their decisions (McNulty, 2012).

In 2007 an advisory non-departmental public body on Antimicrobial Resistance and Healthcare Associated Infection (ARHAI) was created to replace the Specialist Advisory Committee on Antimicrobial Resistance (SACAR). ARHAI has promoted significant improvement in antimicrobial stewardship in the UK by launching the Start Smart-Then Focus (SSTF) approach in 2011 to promote stewardship activities in secondary care and highlights the role of pharmacists in this process (Department of Health, 2011). In 2013, ARHAI launched a report entitled ‘Antimicrobial Prescribing and Stewardship Competencies’ (Department of Health and Public Health England, 2013). These prescribing competencies report describes the

knowledge, skills and behaviours that medical and non-medical independent prescribers should possess to ensure effective antimicrobial stewardship.

In 2013, the annual report (Chief Medical Officer, 2011) by the Chief Medical Officer, Dame Sally Davies, was published which addressed four broad areas including: concern about global AMR, improving awareness and education about AMR, the need to improve surveillance and diagnostics. In September 2013, the Chief Medical Officer of the Department of Health and the Chief Veterinary Officer of the Department for Environment, Food and Rural Affairs (DEFRA) co-authored a strategy report entitled ‘the UK five-year antimicrobial resistance strategy 2013 to 2018’ (Department of Health and DEFRA, 2013). The strategic aims of this strategy are to improve the knowledge and understanding of AMR, conserve the effectiveness of existing treatments and stimulate the development of new antibiotics and diagnostics. The strategy proposed a set of key areas for actions including i) improving infection control, ii) promoting better prescribing, iii) improving education and training, iv) developing new drugs and diagnostics, v) improving access to surveillance data, vi) identifying and prioritizing AMR research needs and vii) strengthening international collaboration.

1.10 Antimicrobial stewardship

Because of AMR and resulting increased mortality and morbidity, and increasing prescribing cost, the Infectious Disease Society of America (IDSA) and Society for Healthcare Epidemiology of America published guidelines to optimise the use of antibiotics and contain AMR (Dellit et al., 2007). Antimicrobial stewardship is defined as interventions designed to improve and measure the appropriate use of antimicrobials by promoting the optimal usage of dosing regimen, dose, choice of antimicrobial and duration. The recommended strategies of antimicrobial stewardship are shown in table 7.

Table 7: Antimicrobial stewardship strategies

Core strategies	Supplemental strategies
Formulary restriction and pre-authorisation	Streamlining, timely de-escalation of therapy
Prospective audit with intervention and feedback	Dose optimisation
Multidisciplinary stewardship team	Parenteral to oral conversion
	Guidelines and clinical pathways
	Education
	Computerised decision support systems
	Laboratory surveillance and feedback
	Combination therapy
	Antimicrobial cycling

Adapted from Dellit, 2007

1.11 Health Information Technology

Efforts to computerise aspects of healthcare started in the 1960s (Greenes, 2014). Yet the rate of adoption and extent of impact of HIT has remained low. Despite the passage of time, HIT has not had the impact anticipated. Health care professionals face a number of challenges including making difficult diagnosis, minimizing errors, saving money and ensuring the provision of high quality care. Yet the need for HIT interventions is now greater than ever. HIT is now seen as a way to help health care professionals do their job effectively. The establishment of the International Medical Informatics Association (IMIA), an independent organisation founded in 1989, is further evidence of the drive toward HIT (Mantas et al., 2010). IMIA plays an integral role in the application of HIT interventions in the fields of healthcare.

The adoption of HIT has relied on national healthcare systems. In the late 1990s, US Government Agencies began to embrace the potential of electronic prescribing systems to

minimise clinical risks in secondary care. In 1999 and 2001, the US Institute of Medicine (IOM) issued two reports which examined how technology could be utilised to improve patient safety (Kohen L.T., 1999, IOM, 2001).

The UK was one of leaders in HIT with early work in the 1950s and 1960s by Hollingsworth and Macfarlane, respectively (Hollingsworth, 1959, Macfarlane et al., 1969). However, HIT interventions have not diffused as extensively into hospital practice in the UK as they have in the US. In 1998, the Department of Health published the first report to present HIT strategy for England, *Information for Health* (National Health Services Executive, 1998). The overall aim of this report was to outline a strategy for developing unified electronic health records (EHRs) ensuring anytime access to patient records, and information to foster best clinical practice for all healthcare professionals working in the NHS. In July 2004, the Department of Health created a new organisation known as NHS Connecting for Health (NHS CFH) which had the responsibility of delivering the National Programme for Information Technology (NPfIT). In 2003, NPfIT started planning for one of the most important HIT interventions namely electronic prescribing with integrated decision support functionality. The extent of use of electronic prescribing in primary care has been more than within hospitals in the UK (Black et al., 2011). Electronic prescribing with its built-in decision support functionalities represents one of the NHS CFH's key interventions to minimise harm and improve patient safety.

1.11.1 Development of electronic prescribing and CDSS in the US and UK

Much of the evidence of the benefit of electronic prescribing originates from the United States. Electronic prescribing systems have been adopted more widely in the US. Commercial electronic prescribing systems in the US differ in the level of advanced functionality they offer, in particular decision support. In the US, CDSS have been used by health care professionals at the point of care for many years and have been extensively evaluated in the medical literature

(Holstiege et al., 2015, Garg et al., 2005, Moja et al., 2014, Baysari et al., 2016, Bright et al., 2012, Curtis et al., 2017).

An early implementation of electronic prescribing was the system at Brigham and Women's Hospital, Boston in the early 1990s (Teich et al., 1992, Bates et al., 1998, Bates et al., 1999, Goundrey-Smith, 2012). The prescribing function was part of an in-house information system, the Brigham Integrated Computing System (BICS). It included formulary prescribing menus, drug interaction checking, and display of relevant laboratory results (Goundrey-Smith, 2012).

Another notable centre for electronic prescribing use in the US is the Wishard Memorial Hospital, Indianapolis, Indiana which was implemented in the 1980s (Tierney et al., 1993 Goundrey-Smith, 2012). The system known as the Regenstrief Medical Record System consisted of a network of computers through the wards and emergency department of the hospital (Goundrey-Smith, 2012). This system enabled electronic ordering and decision support on each ward and electronic transmission of orders to pharmacies.

Electronic prescribing was also developed as the Health Evaluation through Logical Processing (HELP) system of LDS hospital in Salt Lake City, USA (Pestotnik et al., 1996, Pestotnik et al., 1990, Classen, 1998, Goundrey-Smith, 2012)). One of its applications the Antibiotic Assistant provides data necessary to make informed decisions related to antibiotic prescribing.

In the UK, the adoption of electronic prescribing is widespread, although often only in certain clinical areas and for certain types of prescribing (Ahmed et al., 2013). In a recent survey of 101 English hospitals, seventy (69%) hospitals had at least one form of electronic prescribing implemented (Ahmed et al., 2013). More than half (59%) of hospitals with electronic prescribing had more than one system in use (Ahmed et al., 2013). The most notable earliest adopters of electronic prescribing in England are the Wirral Hospitals, in Cheshire, England,

the Burton Hospitals, Burton on Trent, Staffordshire, England and the Royal Hampshire County Hospital, Winchester, England (Goundrey-Smith, 2012).

The Wirral Hospitals started implementing their electronic prescribing system as part of a hospital information system (Chisholm et al.) in 1992. A large study by Pirmohamed and co-workers included patients from Wirral hospital and Liverpool for adverse drug reactions (Pirmohamed et al., 2004). There were 1225 admissions related to an adverse drug reaction, giving prevalence of 6.5% with the adverse drug reactions, directly leading to the admission in 80% of cases. The Burton Trusts has had electronic prescribing since 1992. Queen's Hospital, Burton had a system installed by Meditech which was a US developed product and implemented the pharmacy software of the Meditech system in 1992 (Goundrey-Smith, 2012). In 1996, a rule-based electronic prescribing system had been developed at the renal unit of Queen Elizabeth Hospital, Birmingham, England (Nightingale et al., 2000). The system was able to handle data such as allergies and renal function calculations, laboratory results and diagnosis. Later, this was replaced by the Prescribing Information and Communication System (PICS) (Goundrey-Smith, 2012)

.Table 8: Reported rates of implementation of CDSS in the UK and US in at least one ward or hospital

Decision support	UK rates (Greenes, 2014)	US rates (Jha et al., 2009)
Drug-allergy alerts	35%	61%
Clinical guidelines	29%	27%
Drug-drug interaction alerts	23%	61%
Drug dosing support (renal dose guidance)	21%	46%
Drug-lab test interaction alerts	19%	48%
Clinical reminders	13%	34%

Adapted from (Greenes, 2014)

1.11.2 Motivation for electronic prescribing and CDSS

Evidence has shown that a promising potential of electronic prescribing and CDSS is to optimise patient care and minimise harm. Patient safety is the core driver for the development

and implementation of electronic prescribing (Agrawal 2009). The motivations for electronic prescribing may include:

- Minimisation of the number of medication errors
- Improving documentation and communication about medication
- Providing information at the point of care
- Enforcing policies, formularies and evidence-based guidelines
- Cost reduction

1.11.3 Electronic prescribing

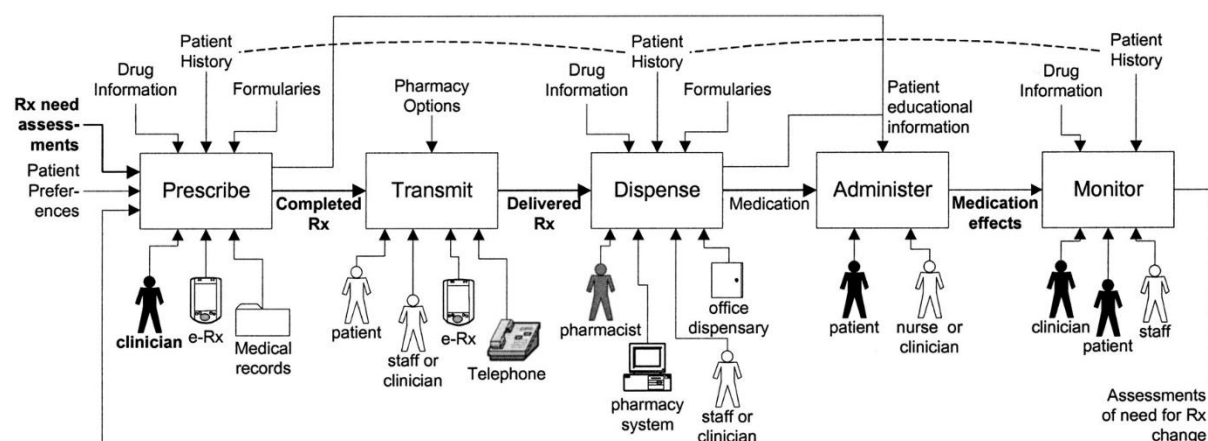
Evidence shows that prescribing errors are very common and are responsible for patient morbidity and mortality. A recent study showed that patients with harm because of medication errors are hospitalised and one in seven hospitalised patients experience prescribing related harm (Pirmohamed et al., 2004, Davies et al., 2009). A study by Davies and co-workers evaluated patients from the Royal Liverpool hospital for adverse drug reactions, 545 experienced one or more adverse drug reactions. The patients experiencing adverse drug reactions were more likely to be older, female, taking a larger number of medicines, and had a longer length of stay than those without adverse drug reactions (Davies et al., 2009). The widespread use of medications coupled with their interaction with patient-related factors and other prescribed medications make it difficult for clinicians to rely on their memory when prescribing medications. Electronic prescribing is a promising solution to help clinicians to choose the most suitable treatment and minimize prescribing errors.

NHS Connecting for Health defined electronic prescribing as “the utilisation of electronic systems to facilitate and enhance the communication of a prescription or medicine order, aiding the choice, administration and supply of a medicine through knowledge and decision support

and providing a robust audit trail for the entire medicine use process’’ (Connecting for health, 2008).

Electronic prescribing can provide decision support for prescribers. Computerised physician order entry (CPOE) can provide physicians with drop-down menus to support prescribing decisions (Black et al., 2011). Such a decision support functionality utilises patient related information and tailors prescribing advice decisions accordingly. Electronic prescribing includes a wide array of systems integrated including CPOE, CDSS and EHR (Black et al., 2011). Electronic prescribing involves the electronic transmission of prescriptions which may include point of care decision support. Electronic prescribing is complex as shown in figure1 because of the diversity of their implementation and the wide arrays of systems that may need to be integrated. Electronic prescribing systems can involve many health care professionals at different points in the prescribing pathway. This may require health care professionals to access information along the prescribing process to adjust prescribing accordingly. Prescribing errors can occur at any point of the prescribing process.

Figure 5 Complexity of electronic prescribing architecture



Adapted from (Bell et al., 2004 and Sheikh, 2011)

1.11.4 Computerised decision support systems (CDSS)

CDSS are computer systems that integrate patient information with knowledge bases to provide intelligently filtered decision support recommendations at the point of care in the form of alerts, reminders and recommendations. Wyatt and Spiegelhalter's definition of CDSS is “active knowledge systems which use two or more items of patient data to generate case-specific advice” (Wyatt and Spiegelhalter, 1991).

CDSS are diverse and differ in system and design. They can be integrated with other systems and used by many health care professionals involved in the prescribing process. The involvement of healthcare professionals in the use of these systems can be active or passive (Black et al., 2011). The knowledge bases used with electronic prescribing systems can be purchased commercially or can be locally developed. CDSS help clinicians to make informed decision given the highly complex nature of clinical knowledge. Knowledge base can fill in the gaps in clinicians' knowledge and help in processing patient information to provide better decision making. Therefore, CDSS have the potential to improve the efficiency and effectiveness of prescribing and improve the quality and safety of healthcare. CDSS can be used for a variety of applications ranging from diagnostic, preventive and therapeutic purposes. They can also be used in research studies to identify patients who may need specific care according to treatment research protocols.

1.11.5 Types of IT interventions to improve antibiotic prescribing

The most common IT interventions designed to improve antibiotic prescribing are standalone CDSS, electronic prescribing with embedded decision support, computerised approval systems and surveillance systems (Baysari et al., 2016). Most CDSS use patient-related information to suggest appropriate antibiotics. The most common functions of CDSS are as follows (Baysari et al., 2016):

- ‘Automatically uses or displays patient specific pathology/microbiology information’

- ‘Recommends appropriate antibiotic treatment’
- ‘Present passive information such as guidelines and antibiotic resistance profiles’
- ‘Includes computerised alerts’
- ‘Allow antibiotics to be ordered from within CDSS
- ‘Requires prescribers to enter a reason for not ordering recommended antibiotics’

The most common functions of electronic prescribing with embedded decision support are as follows (Baysari et al., 2016):

- ‘Requirement to select indication for antibiotic use’
- ‘Pre-written/default orders, order sets or components’
- ‘Computerised alerts’
- ‘Passive information (guidelines)’
- ‘Dose calculation’

The main functions of computerised antibiotic approval systems are as follows (Baysari et al., 2016):

- ‘Linked to electronic health record or electronic prescribing for direct import of patient information’
- ‘Decision support such guidelines’
- ‘Automatic approval for certain indications’

The main functions of surveillance systems are as follows (Baysari et al., 2016):

- ‘Generates a report of potentially inappropriate antibiotic use for pharmacy’
- ‘Generates a report of potentially inappropriate antibiotic use for infectious diseases staff’
- ‘Alerts pharmacy via paging or computer of potentially inappropriate antibiotic use’

- ‘Alerts infectious diseases staff via computer of potentially inappropriate antibiotic use’

1.11.6 Implication of health information technology for antibiotic prescribing

The goal of prescribing antibiotics is to choose the most suitable agent for a given patient.

Antibiotic prescribing is a multi-step process including:

- Confirming the diagnosis of infection and its risk assessment,
- Initiation of antibiotic treatment,
- Selection of the most appropriate antibiotic and making a decision on dose, route, frequency and duration,
- Monitoring for therapy effect and side effects.

The mostly commonly used decision support tools are electronic guidelines and protocols.

Table 4 provides an overview of CDSS used to optimise antibiotic prescribing (Sintchenko et al., 2008).

Table 9: Decision support for antibiotic prescribing

Type of antibiotic prescribing	Task of antibiotic prescribing	Decision support type
Microbiology result-independent (empirical) prescribing	Infection risk assessment	Probability calculators
	Assessment of possible antibiotic resistance profiles’	Interactive interface providing local cumulative antibiotic resistance data
	Choice of therapies	Electronic guidelines and protocols
	Approval for prescribing and auditing use of restricted antibiotics’	Automated antibiotic approval for common evidence-based indications
	Ordering	Computerised physician order entry often linked to medication lists and electronic protocols
Microbiology result guided prescribing	Initiation of therapy and therapy adjustment	Real time access to laboratory data through portable computers
	Choice of therapies	Computer-based monitoring, alerts to critical laboratory results and potential drug interactions
	Monitoring of therapies	Reminders about discrepancies between prescribed antibiotics and culture susceptibility results

Adapted from (Sintchenko et al., 2008)

The target functional requirements for a comprehensive CDSS should be based on the Centre for Disease Control and Prevention (12-step) programme to contain AMR among hospital patients (Pestotnik, 2005)

Table 10: Functional requirements of clinical decision support systems in relation the 12-step programme to combat antimicrobial resistance

Step and Description	Clinical decision support system requirements for each step
Prevent infection 1. Vaccinate 2. Remove catheters	Vaccination reminders Catheter extended-use alerts
Diagnose and treat infections effectively 3. Target the pathogen 4. Access the experts	Drug-bug mismatch alerts Drug spectrum alerts Infer infections Timing-of-therapy alerts Timing of prophylaxis alerts Drug dosage alerts Recommend infectious disease consultation when appropriate
Use antimicrobials wisely 5. Practice antimicrobial control 6. Use local data 7. Treat infection not contamination 8. Treat infection not colonization 9. Know when to say no to vancomycin 10. Stop treatment when infection is cured or unlikely	Parenteral-to-oral switch alerts Automated formulary checking Automated recommendations for defined infections Automated recommendations for prophylaxis Evidence-based knowledge bases Automated antibiograms Automated empiric recommendations Track and alert on emerging resistance Infer contamination of specimens Infer colonization Target-drug alerts Duration-of-therapy alerts Duration-of-prophylaxis alerts
Prevent transmission 11. Isolate the pathogen 12. Break the chain of contagion	Patient isolation alerts Infection control precaution reminders Health care-associated infections case-finding alerts Patient-based location tracking Population-based location tracking Clonal detection and alerting Target-organism alerts Hand-washing reminders Online infection control information

Adapted from (Pestotnik, 2005)

1.11.7 Birmingham Prescribing Information and Communication System (PICS)

University Hospital Birmingham Foundation Trust (UHBFT) is one of the leading academic medical centres in the West Midlands. One of the IT programmes UHBFT has introduced is the Prescribing Information and Communication System (PICS). PICS is a home-grown, rule-based electronic prescribing system that provides at the point of care checks for allergies, drug interactions, dose limits, allergies and contraindications (Slee, 2010). The system has over 4,000 registered users and manages over 25,000 prescriptions and 125,000 drug administration events a week. PICS has been in use for over ten years and has been implemented to cover both inpatients and outpatients.

The system screens each decision made by clinicians through an error filter such as amending a patient's therapy, ordering tests and discharge. The system automatically saves the decision and either confirms the order, alerts the clinician of the potential error, requests their password to acknowledge the decision they have made and take responsibility for it, or stops the order. The system also amends patient care such auto-prescribing for MRSA eradication therapy after a positive swab skin test. The system also displays drug chart and flowsheet of each patients.

The use of PICS has improved the quality of health care at UHBFT. The system reduced omission rates from 10.3 to 4.4% for antibiotics and from 16.4 to 8.2% for non-antibiotics across the intervention period. The system reduced total medication errors by 57% for antibiotics and by 50% for non-antibiotic drugs (Coleman et al., 2013). Our study differs from the work of Coleman that we evaluated the impact of structured prescribing on the volume of antibiotic use measured in DDD/1000 bed days while his study evaluated the impact of PICS on the omission rate for antibiotics and non-antibiotic medications. Coleman study did not evaluate the impact of structured prescribing and the focus was on the impact of PICS in reducing omission rate. The main outcome of Coleman study was the percentage of missed

medication doses. His study showed that electronic prescribing systems can facilitate data collection relating to missed medication doses.

1.11.8 Structured prescribing

Structured prescribing is an algorithm-directed, guideline-based tool embedded within PICS for prescribing antibiotics. It was designed to optimise the empirical use of antibiotics, was first launched in 2008. Given the system's poor layout and hindrance of work flow it was taken out in 2014. Several changes have been made since it was taken out to make the system layout better and compatible with work flow. It incorporates patient characteristics including kidney function, weight, allergies and provide an intelligently filtered decision of antibiotic regimen at the point of care. The desired goals of structured prescribing are as follows:

- Avoiding errors in dose range checking
- Avoiding drug interactions
- Avoiding errors in renal dosing
- Avoiding errors in allergy checking
- Enforcing compliance with policy and antibiotic prescribing guidelines
- Containing AMR
- Reducing the volume of antibiotic use and optimise the safe and effective use of antibiotics

Structured prescribing can be accessed through a screen at PICS (See figure 10). All what should be done is to click on Structured Prescribing button at the bottom left corner of the screen. Then another screen will be displayed with drop down menus to select the indication and the severity or type of infection for which antimicrobial treatment is required (See figure 11). After the indication or the severity of infection has been chosen, subsequent questions may be asked related to patient including GFR, allergies, body weight and kidney function. Then a

treatment regimen can be displayed taking in consideration patient specific factors. After receiving the treatment, Structured Prescribing may alert the prescriber about the duration of course of treatment. Figure 12 shows an alert triggered for patient receiving metronidazole for the treatment of *Clostridium difficile*. The patient was on metronidazole for 5 days and test results remained positive for *Clostridium difficile*. Trust guidelines suggested switch to an alternative therapy because metronidazole failed to treat the infection

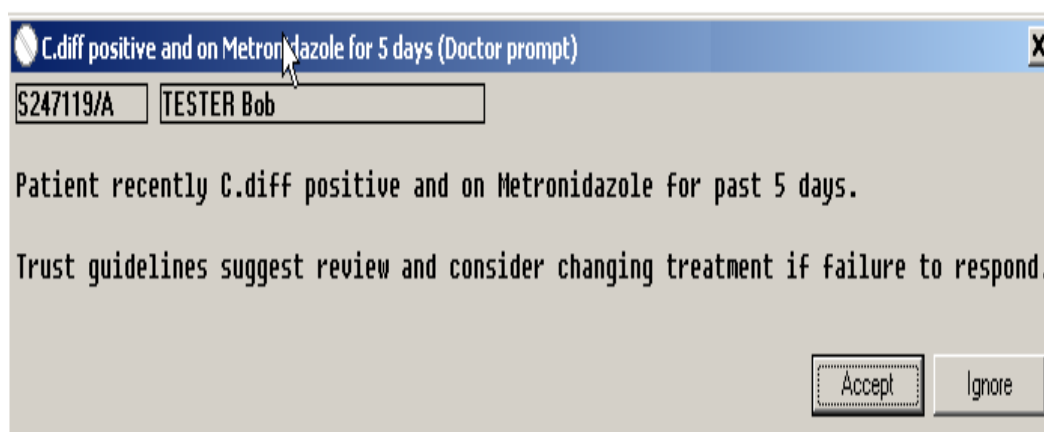
Figure 6: Screen showing how to access Structured Prescribing protocols for antimicrobials

The screenshot shows the 'Add Regular prescription' window. It has a 'Drug' dropdown menu, a 'Find' button, and a 'BNF' button. Below these are tabs for 'Main' and 'Alternative'. The 'Main' tab is active, showing fields for 'Route', 'Form', 'Dose', and 'Units'. To the right of these are fields for 'Frequency', 'Duration' (set to 'unlimited'), and 'Start at/after'. Below the 'Main' tab are buttons for 'Review', 'Scale', 'Formula', 'View Scale...', and 'View Formulas'. At the bottom, there is a checkbox for 'Additional One Off' with 'Yes' and 'No' radio buttons, and buttons for 'Tick off All', 'Cancel', and 'OK'. A 'Jump to Structured Prescribing' button is located at the bottom left. A 'Please Note' message states: 'Drug proposals based on UHB antibiotic prescribing guidelines are available via the Structured Prescribing module'. On the right side, there is a table with 'Times' and 'Due' columns, listing times from 02:00 to 22:00.

Figure 7: Screen showing drop menu of order sets for prescribing antimicrobials

The screenshot shows the 'Select Structured Prescription' dropdown menu. The menu is open, displaying a list of order sets for 'Clostridium difficile associated diarrhoea'. The first item is 'Gastrointestinal', which is highlighted. Below it are several options: 'Mild/moderate 1st occurrence or 1st recurrence', 'Mild/moderate 1st occ/ 1st rec no better after 5d', 'Mild/moderate 2nd recurrence', 'Severe; 1st occurrence, 1st or 2nd recurrence', and '3 or more C. diff disease recurrences'. A mouse cursor is pointing at the 'Gastrointestinal' option.

Figure 8: Alerts for antimicrobial therapy to be reviewed by doctors



1.11.9 Role of pharmacy in the context of electronic prescribing

Dispensing the appropriate medications, patient counselling and ensuring the correct use of medications and their timely supply are all elements of daily pharmacy work (Connecting for Health, 2014). Electronic prescribing can support all of these activities and pharmacist has an integral role in ensuring that electronic prescribing is safe and efficient. Pharmacists can play a major role in the early phases of development and implementation of electronic prescribing systems given their knowledge with medicines and experience with technology (Connecting for Health, 2014). Pharmacists have a broad experience with computers including stock control and using robots to dispense medications (Connecting for Health, 2014).

Electronic prescribing change the way pharmacists do their job and create new opportunities to develop their professional role (Connecting for Health, 2014). It has been shown that pharmacists embrace electronic prescribing evidenced by the positive aspects they report including: legible prescriptions that require less interventions, no chart chasing, improved interaction with other health care professionals, and better discharge planning (Connecting for Health 2014). It is noteworthy that after implementing electronic prescribing, pharmacists are able to change their focus towards new issues such as prescribing difficult medications (e.g. sliding scale use of insulin and heparin), enforcing policy and prescribing guidelines, creating

structured prescriptions and utilising new opportunities for information retrieval and research (Connecting for Health, 2014).

Among the issues of planning of electronic prescribing and pharmacy involvement that need to be addressed are: how electronic prescribing system is chosen, set-up and tested, the way the implementation will be carried out and accomplished safely, how training will be organized, the types of services pharmacist will provide during the implementation phase and other subsequent phases, the way data produced by the electronic prescribing system is utilised to improve research and optimise the rationale use of medicines (Connecting for Health, 2014). Another major part pharmacists play is organising and preparing training (Connecting for Health, 2014). The role of pharmacy will be explored further as we move along the work packages of this research.

Chapter 2: The Programme of Work

2.1 Introduction

The overall study design, rationale for and the detail the methods used in each part of the research are described in this section. The main elements of the research were a systematic review and meta-analysis of the literature together with, qualitative and quantitative analysis of antibiotic use in a secondary care environment utilising an electronic prescribing system.

2.2 Evolution and development of the study aims

Most of the research on electronic prescribing of antibiotics has been conducted in primary care settings (Holstiege et al., 2015). Many questions concerning the impact of electronic prescribing and CDSS on antibiotic use in hospitals remained unanswered. Therefore, this programme of work was undertaken to examine the impact of CDSS on antibiotic use in a hospital setting by measuring specific outcome measures from an electronic prescribing system.

2.3 Research rationale

The overall purpose of the present research is to examine the empirical evidence of the impact CDSS on antibiotic use in the hospital inpatient setting, to explore views of medical and non-medical independent prescribers toward CDSS, and to assess the impact of CDSS on specific outcome measures related to antibiotics.

The focus of the project was an NHS Trust in the West Midlands, University Hospital Birmingham Foundation Trust (UHBFT). The literature on CDSS, their impact on practitioner performance and patient outcomes in England is sparse. There is no clear evidence that CDSS are effective in optimising antibiotic use at the point of care and minimising AMR in the inpatient setting in England. To date, there is little published research on the impact of CDSS on practitioner performance and patient outcomes, and the impact of paper-based and computer-based CDSS on antibiotic use in the primary care setting. Additionally, there is no

structured, coordinated monitoring or evaluation of the ability of CDSS to minimise AMR and optimise antibiotic use.

The perceptions and attitudes of medical and non-medical independent prescribers regarding their needs when utilising computerised systems for antimicrobial prescribing where improvement is required, and the type of improvements needed are relatively unclear. Given the increased interest in utilising health information technology (HIT) such as CDSS within the NHS, it is paramount to understand how independent prescribers use and perceive CDSS, and examine their impact on optimising antibiotic use in the hospital inpatient setting.

2.4 Thesis layout

In the light of official concerns over AMR and the rational use of antimicrobials, the present research was designed to examine the impact of CDSS on antibacterial use in the hospital inpatient setting. This thesis describes the current maturity of CDSS both within the UK and globally by focusing on contemporary areas of concerns. This programme of work evaluated a CDSS tool ‘Structured Prescribing’ in order to optimise empirical antimicrobial prescribing in the hospital in-patient setting. The programme of work was conducted over three research work packages.

The first research work package had the aim of examining the impact of CDSS on antibacterial prescribing. Given the weakness and paucity of evidence, and the scarcity of reviews in this research area, it was decided to conduct an international systematic review and meta-analysis aimed to review the current state of evidence on the impact of CDSS on antibacterial use in the hospital inpatient setting.

The second research work package was quantitative in nature and designed to assess attitudes, perceptions and views of medical and non-medical independent prescribers towards CDSS

within University Hospitals Birmingham NHS Foundation Trust (UHBFT). It was decided to conduct one online, self-completed questionnaire within UHBFT.

The third research work package was quantitative in nature and consisted of conducting a retrospective before-and-after study to measure the impact of 'Structured Prescribing' on the volume of antimicrobials used and adherence to decision support recommendations. Data was obtained from the electronic prescribing system within UHBFT, the Prescribing Information and Communication System (PICS), before and after the deployment of Structured Prescribing. The quantitative work package was important because it would provide evidence for the effectiveness, clinical appropriateness and safety of CDSS in optimising antibacterial use in the inpatient setting.

2.5 Research Questions, Aims, Objectives and Hypothesis

2.5.1 The research questions below were addressed:

What is the state of evidence of the impact of CDSS on antibiotic use in hospital settings?

What are the effects of CDSS on antibiotic use in a hospital setting?

What are the perceptions and attitudes of medical and non-medical health care professionals towards CDSS?

What is the impact of CDSS on the volume of antibiotic usage?

What is the impact of CDSS on the defined daily doses of all antibiotics and selected ones?

2.5.2 Aims

To investigate the effect of computerised decision support on antibiotic prescribing in secondary care. The project will determine if using a computerised decision-making approach would produce better outcomes than paper-based systems.

2.5.3 Objectives

- To undertake a systematic literature review and meta-analysis designed to examine the impact of electronic decision support systems on antibiotic use in secondary care.
- To undertake a qualitative survey to identify CDSS design features, knowledge base requirements and human factors essential for successful CDSS development, implementation, deployment and uptake.
- To conduct a retrospective before and after study to measure the impact of CDSS on the volume of antibiotic use in a specific hospital site.

2.5.4 Hypothesis

It was hypothesized that a CDSS known as ‘Structured Prescribing’ built in the PICS system would produce better outcomes of antibiotic prescribing compared to traditional electronic prescribing approaches. Structured prescribing is an algorithm-directed, guideline-based prescribing of antibiotics. It was designed to optimise the empiric use of antimicrobials in the management of infections.

2.6 Systematic review and meta-analysis

Systematic reviews are a type of literature review where multiple studies may be grouped and analysed in a systematic format. Systematic reviews differ from traditional narrative reviews in many ways. Narrative reviews tend to be descriptive and do not entail a systematic search of the literature. Narrative reviews are informative but often include an element of selection bias (Uman, 2011). Systematic reviews usually involve a comprehensive search strategy

designed to reduce bias by locating, assessing and synthesizing all relevant studies on a certain topic (Uman, 2011). In addition, many narrative reviews may not assess the methodological quality of included studies leading to the inclusion of low quality studies. Quality assessment is an integral stage of the systematic review process. It is usually conducted to examine the validity of evidence. Quality assessment may occur at different stages of the systematic review during the application of inclusion and exclusion criteria, as well as data extraction and during data synthesis. There are a number of quality assessment tools available to check quality of evidence for systematic reviews (Centre for Reviews and Dissemination, 2008, Higgins, 2011). However, the lack of consensus of which tool to use and which threshold to apply for inclusion criteria makes it difficult to decide which tool to adopt. The stages of developing a systematic review and meta-analysis are presented in table 11.

Table 11: Stages of developing a systematic review and meta-analysis

Stage	Explanation
Formulate the review question	This stage involves defining the review question, forming hypotheses, and developing a review title
Define inclusion and exclusion criteria	The Cochrane acronym PICO (population, intervention, comparison, outcomes) is useful to determine the inclusion criteria for the review
Develop search strategy and locate studies	Designing key terms related to the PICO question to be able to identify all relevant trials
Select studies	After retrieving a list of abstracts all related studies would then be obtained and reviewed in full
Extract data	Create a simple extraction form to organize the information extracted from each reviewed study
Assess study quality	Utilising quality assessment tools to assess the quality of included studies
Analyze and interpret data	There are many various statistical programs available to calculate effect sizes for meta-analyses
Disseminate findings	Publishing reviews in academic journals
Adapted from (Higgins, 2011)	

Systematic reviews may also include meta-analysis of the findings which involves use of statistical techniques to synthesize the data from many studies into a single quantitative estimate or summary effect size.

One goal of meta-analysis is to estimate the overall or combined effect. When the effect size is consistent from one study to the next, meta-analysis can be used to identify this effect. There are two popular statistical models for meta-analysis, the fixed-effects model and the random-effects model. Under the fixed-effects model, it is assumed that there is one true effect size that underlies all of the studies in the analysis, and the only reason that the effect size varies between studies is random error. Under the random-effects model, the true effect size might vary from one study to another and the aim is to estimate the mean of a distribution of effects. The type of effect size measured normally depends on the type of outcome and intervention being assessed. Some common examples include Odds Ratio (OR), weighted/standardized mean differences (WMD, SMD) and Relative Risk or Risk Ratios (RR). Table 12 shows the differences between the fixed-effects model and the random-effects model (Higgins, 2011).

Table 12: Fixed-effect model vs random-effect model

Fixed-effect model	Random-effect model
Yields more precise estimate of the combined effect	Yields less precise estimate of the combined effect
Narrow confidence intervals	Wide confidence intervals
We assume that the true effect size for all studies is identical	We assume that the true effect size for all studies is not identical and the goal is to estimate the mean of a distribution of effects
Higher combined effect if larger studies have high effects	Lower combined effect if the larger studies have high effects
Lower combined effect if smaller studies have high effects	Higher combined effect if smaller studies have high effects

Adapted from Higgins, 2011

2.7 Electronic questionnaires

Questionnaires are used to collect information from the respondents to answer the research questions. A questionnaire is an easy way of gathering information from a large number of

people within a period of time (Jenn, 2006). Electronic questionnaires were chosen for the survey undertaken as part of this programme of work. Electronic questionnaires are flexible, simple and cost-effective and are generally located in one place and have minimal distribution costs (Van Selm and Jankowski, 2006). They are similar to mail surveys in that they are utilised to obtain detailed user characteristics and satisfaction feedback. One advantage of these questionnaires is that they are located in one place so there are no distribution costs. Table 13 lists the advantages and disadvantages of electronic surveys (Jenn, 2006, Van Selm and Jankowski, 2006). One potential disadvantage of an electronic survey is that respondents' views may not represent those of the wider population.

Table 13: Advantages and disadvantages of online questionnaires

Advantages	Disadvantages
Relatively easy to administer	Respondents may not feel encouraged to provide honest, accurate answers
Can be developed in less time	Respondents may not comfortable to provide answers that present themselves in an unfavourable manner
Cost effective but cost depends on survey mode	Survey with closed ended questions have lower validity rates than other types of question types
Can be administered remotely via email, online	Data errors due to question non-responses may exist
Conducted remotely can reduce geographical dependence	Customised surveys can run
Capable of collecting data from a large number of respondents	Data error due to question non-responses may exist
Flexibility of asking questions	Customised surveys can cause the risk of errors
A broad range of data can be collected	
Standardized survey are free from several types of errors	
A wide range of data can be collected (beliefs, opinions, attitudes.....etc).	

Adapted from (Van Selm and Jankowski, 2006)

There are two types of electronic questionnaires. Online questionnaires uploaded to a website where the participant is invited to complete the questionnaire online (McPeake et al., 2014). Other electronic questionnaires are embedded in the text of an email or are presented as a link attached to an email (McPeake et al., 2014). One of the major issues with electronic surveys is securing an up-to-date and correct email address for potential respondents. Email addresses for individuals and institutions may change and may remain appropriate for a limited period of

time. Another potential problem may be that individuals can have more than one e-mail address and may rarely check all accounts. Low response rates are a potential issue with electronic surveys. Response rates of electronic surveys may be lower than expected for the following reasons:

- The population being researched,
- Lack of familiarity with using the website,
- Inconsistent reliability of internet access,
- Lack of trust in technology particularly when communicating confidential issues.

Table 14: Key strategies in conducting online questionnaires

<ul style="list-style-type: none"> • Personalize the email to each individual participant • If an email is returned undeliverable, ensure that the institution has not changed its standard email address. • Sending two reminders reporting response rates and setting goals • A clear and comprehensive instructions of how to complete the questionnaire especially if it is very short, tell the respondent how quickly it can be completed. • To ensure ease of response, embed the link of the questionnaire within the invitation letter rather than adding it as attachment.

(Jenn, 2006, Van Selm and Jankowski, 2006).

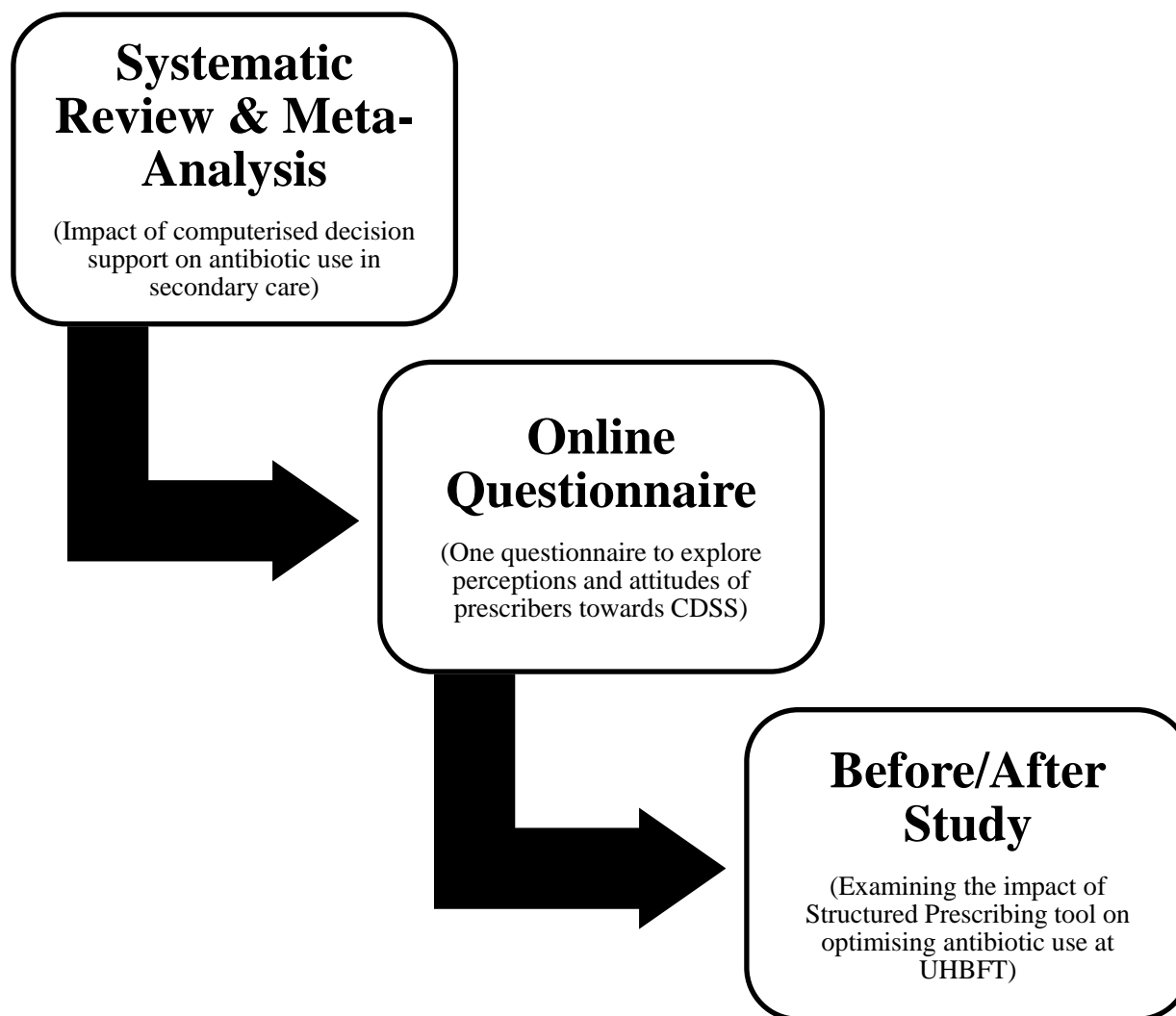
2.8 Before and after study design

A before-and-after study is a study in which outcomes are measured before an intervention is conducted and compared with outcomes measured afterwards (Thiese, 2014). A before-and-after study design measures the occurrence of an outcome before and after an intervention is conducted (Thiese, 2014). Before-and-after studies may be single arm, one group measure before and after or multiple arms, where there is a comparison between groups (Thiese, 2014). Usually, there is one arm with the intervention called the control arm. However, one of the weaknesses of this type study is that there is no control over potentially confounding elements that are changing at the same time the intervention is conducted (Thiese, 2014). Outcomes for

before-and-after studies can be binary such as incidence or prevalence or continuous such as heart rate or blood pressure. The analysis of this type of study depends on the outcome being assessed. For the purpose of the present research, it was decided to adopt the before-and-after study design to examine the impact CDSS intervention on defined daily doses of antibiotic prescribed using time as the independent variable.

The following figure represents an overview of the work packages undertaken in this research.

Figure 9: A diagram of the work packages involved in this thesis



2.9 Study setting

The questionnaire study and the before-and-after study were conducted in the University Hospital Birmingham NHS Foundation Trust (UHBFT). UHBFT is a large university teaching hospital in the West Midlands of England. UHBFT is a leading centre for cancer management, solid organ transplantation and renal dialysis. It provides specialist cardiac and liver services and has a centre for burns and plastic surgery (UHBFT, 2017). UHBFT has 1213 beds including 100-bed critical unit and employs 9000 staff (UHBFT, 2017). UHBFT has a further 170 beds and a second ambulatory care unit in order to cope with the growing demand of increased patient numbers. UHBFT has an Institute of Translational Medicine where cutting edge research from the University of Birmingham may be transferred into enhanced treatment for patients (UHBFT, 2017). In recent years UHBFT has been acknowledged as one of the most successful hospital regionally and has been asked to give management support for other hospitals in the area (UHBFT, 2017).

Chapter 3: The impact of computerised decision support systems on antibiotic use in hospitals a systematic review and meta-analysis

Curtis, C. E., Al Bahar, F. and Marriott, J. F. (2017) 'The effectiveness of computerised decision support on antibiotic use in hospitals: A systematic review', *PLoS One*, 12(8), pp. e0183062

3.1 Introduction

Since their introduction as a therapeutic intervention, antimicrobials have saved millions of lives (Filice et al., 2013). Antimicrobial resistance (AMR) has increased over the past four decades (King et al., 2007). Evidence shows that 30%-50% of antimicrobial prescribing is sub-optimal (Dellit et al., 2007). Inappropriate antimicrobial use has been shown to be an important determinant of the emergence and persistence of AMR (King et al., 2007). This pattern of irrational antimicrobial use in hospitals and the relative reduction in development of new antibiotic entities create a challenging situation for clinicians as the options to treat infections, especially those caused by resistant pathogens, become limited.

The use of health information technology (HIT) is one strategy to optimise antibiotic use in health care settings. Over the last twenty years, there have been rapid advances in HIT, increased uptake of the use of computers in healthcare and increased financial investments in HIT. In the United Kingdom, £12.8 billion has been invested in the National Programme for Information Technology (NPfIT) by the National Health Services (NHS) (Black et al., 2011). The NHS has embraced the role of HIT in optimising the quality of care and patient safety. Computerised Decision Support System (CDSS) represents a potential solution for improving antimicrobial prescribing and containing antimicrobial resistance¹ by supporting clinical decision making (Westphal et al., 2011, Calloway et al., 2013) thus optimising antibiotic use and improving patient outcomes. CDSS potentially plays an important role in guiding

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prescribing practices such as antibiotic selection and dosing suggestions, alerting prescribers of potential adverse drug reactions and drug allergies.

Two previous systematic reviews focused on the impact CDSS on antibiotic use in primary care (Holstiege et al., 2015a) and included non-computerised decision support (Shebl et al., 2007). Holstiege and co-workers found that five out of seven studies showed marginally to moderately significant effect of CDSS in improving the clinicians' prescribing behaviour of antibiotics. The study also showed that CDSS that automatically provided decision support were more likely to improve prescribing behaviour than CDSS that had to be activated by prescribers. Shebl and co-workers showed that studies included in the systematic review evaluated different outcomes. Four studies evaluated the process of care and only one study evaluated the cost effectiveness of CDSS as well as patient outcomes. Although the cost of antibiotic decreased using CDSS, there was no change in mortality or length stay for patients. Another more recent systematic review addressed a research question similar to this study and has examined the impact of HIT interventions on antimicrobial prescribing (Baysari et al., 2016). The study by Baysari and co-workers evaluated the impact of CDSS on the appropriateness of antibiotic use, mortality and length of stay. The findings showed that CDSS improved the appropriateness of antibiotic use by improving the adequacy of antibiotic coverage and adherence to guidelines. There was no effect of CDSS on morality and length of stay. The scope, design and timing of these reviews may have excluded relevant CDSS studies that match the inclusion criteria in the current review. The aims of this study were to systematically identify evidence on the impact of CDSS interventions on antibiotic use in the hospital inpatient setting; to conduct a meta-analysis using odds ratio to assess the impact of CDSS on the adequacy of antibiotic coverage and mortality; and to assess the impact of CDSS, using relative differences, on length of stay, volume of antibiotic use, antimicrobial resistance and compliance with guidelines.

3.2 Methods

3.2.1 Data source and study selection

A systematic literature search was conducted utilising eight online databases including MEDLINE, EMBASE, PUBMED, Web of Science, CINAHL, Cochrane Library, HMIC, and PsycINFO. The reason why these databases were chosen is because they are very comprehensive, subject specific and they are related pharmacy practice and evidence based medicine. The search was conducted from inception to 20th of December, 2014. An updated literature search was conducted from January 1st 2015 to October 1st 2016. The search was conducted using a strategy based upon combinations of the following terms: (electronic prescribing) OR (clinical decision support) AND (antibiotic or antibacterial or antimicrobial) AND (hospital or secondary care or inpatient). The key terms were derived from the research question under research. The search strategy is in the appendix.

Titles and abstracts from retrieved references were examined by two reviewers to determine the potential eligibility for inclusion. Any disagreement of the eligibility of inclusion was resolved and consensus was reached by a third researcher. Full texts of potential studies were examined for eligibility against the review inclusion criteria. Bibliographies of retrieved articles, previous systematic reviews and grey literature were examined to identify additional articles that could have been missed by this search strategy.

3.2.2 Inclusion and exclusion criteria

Criteria for inclusion were developed based to the research question of the systematic review and the PICO (Population, Intervention, Comparison, Outcome). Criteria for inclusion in the systematic review were: (i) health care providers in inpatient or ICU or emergency (ED) settings (ii) the intervention involved CDSS aimed at improving antibiotic prescribing at the point of care and (iii) the intervention was compared to no intervention, non-CDSS intervention (non-electronic decision support) or to an intervention with CDSS with different features. For

the purpose of the systematic review, the definition of CDSS by Kawamoto and Bates was adopted and was defined as a computer-based system designed to help directly in clinical decision making in which the characteristics of individual patients are utilised to generate recommendations presented to clinicians at the point of care in a passive or active format such as alerts, reminders and guidelines (Kawamoto et al., 2005, Bates et al., 2003)

Non-electronic decision support studies, non-hospital based studies, qualitative studies, case report, case series studies, conference abstracts, commentaries, and letters, papers examining the performance of the system as opposed to its impact on antibiotic prescribing were excluded. In the case where a study had an unclear inclusion status, conflicts were resolved and consensus was reached by a third reviewer.

3.2.3 Data extraction and quality assessment

A custom data extraction form was created to match the specific needs of the review. According to PICO (Population, Intervention, Comparison, Outcome), data related to study design, participants, interventions, comparators, outcomes, and main findings were extracted by one reviewer and confirmed by another. Disagreements were resolved by consensus, with a third investigator. When studies did not report sufficient data to allow pooling for meta-analysis, results were summarised qualitatively using relative differences. Authors of papers containing insufficient information to be included in the meta-analyses were contacted requesting additional data.

The quality of included studies was assessed using a 10-point rating scale previously used to evaluate CDSS studies (see table 15) (Hunt et al., 1998, Garg et al., 2005, Pearson et al., 2009, Baysari et al., 2016). The scale included five domains (2 points per domain): method of allocation of study groups, unit of allocation, presence of baseline differences between groups, objectivity of outcome measures, and completeness of follow-up for appropriate unit of

analysis. Assessment of the methodological quality of the eligible studies was undertaken independently by two reviewers. Reviewer disagreements were resolved by a third reviewer.

Table 15: Quality assessment tool

Method of allocation of study groups 2= Random, 1= Quasi-random, 0= Selected concurrent controls
Unit of allocation 2= Cluster (e.g. practice), 1= Physician, 0= Patients
Presence of baseline differences between groups 2= No baseline differences present or appropriate statistical adjustments made 1= Baseline differences present and no statistical adjustment made 0= Baseline characteristics not reported
Objectivity of outcome measures 2= Objective outcomes or subjective outcomes with blinded assessment 1= Subjective outcomes with no blinding but clearly defined assessment criteria 0= Subjective outcomes with no blinding and poorly defined
Completeness of follow-up for appropriate unit of analysis 2= >90%, 1= 80-90%, 0= <80%

3.2.4 Data analysis and statistical analysis

A defined set of outcomes essential in estimating the effect of CDSS in optimising antibiotic use shaped the synthesis process. Adequacy of antibiotic coverage and mortality were chosen to be meta-analysed after creating a mind map piloted with many researchers. The choice of outcomes for meta-analyses were influenced by the current literature. Meta-analysis was conducted when studies evaluated the same outcome, and had sufficient data to allow pooling. All studies were eligible for inclusion in the meta-analysis as all assessed the impact of CDSS on antibiotic prescribing in the hospital inpatient setting. The meta-analysis focused on two outcomes: adequacy of antibiotic coverage (13 studies) and mortality (20 studies). Odds ratios and 95% confidence intervals (CIs) were calculated for each trial by reconstructing tables based on the number of patients randomly allocated and the number of patients with the outcome of interest. Inter-study variance was assessed using the τ^2 test. Inter-study heterogeneity was assessed using the χ^2 test and the I^2 statistics. An I^2 value higher than 75% was regarded as ‘significant heterogeneity’ and a value less than 40% was considered ‘not significant

heterogeneity'. Funnel plots were examined for the two outcomes in order to assess potential asymmetry that may indicate publication bias or methodological flaws in small studies. Study results were considered statistically significant if the p value was below 0.05. Based on literature, subgroup analyses were conducted for one methodological factor (Cochrane-compliant design versus non-Cochrane design), one contextual factor (US versus non-US), and one intervention variables (hospital wide versus ICU) (Nuckols et al., 2014, Baysari et al., 2016). Cochrane compliant design studies included randomised controlled trials, controlled before and after studies and controlled interrupted time series. Non-Cochrane studies included uncontrolled before and after studies, cohort studies and case-control studies. Summary estimates were calculated by using the Mantel Haenszel random-effects model (DerSimonian and Kacker, 2007) as implemented in Reviewer Manager ((RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

The calculated heterogeneity of included studies and outcome assessment precluded pooling of data for some outcomes: percentage mean difference analyses of such outcomes were conducted instead. To facilitate comparison across studies, units of volume of antibiotic use were converted to defined daily doses per 1000 bed days (DDD/1000 bed days) while units for drug costs were left in the currency of the country of origin. Compliance with antibiotic guidelines was measured by percentage mean differences between intervention and control groups and length of stay was measured by differences in the number of bed days between intervention and control groups.

3.3 Results

3.3.1 Search results

For the systematic review, the PRISMA statement was adopted; (Moher et al., 2009) see PRISMA flowchart in Figure 10 which shows the results of the search and selection process. After screening 2459 studies, the removal of 237 duplicates between databases, the addition of 18 studies from bibliographies of included studies and previous systematic reviews, and the

addition of 10 studies from the second updated PUBMED search, a total 378 full-text studies were reviewed. Of these, 297 studies did not meet the inclusion criteria for the following reasons: they were not conducted in secondary or tertiary care settings, they did not answer research questions, or they had inadequate study design. The characteristics of the 81 studies which were included are summarized in table 16. Twenty-six studies assessed mortality, 25 assessed length of stay, 19 assessed volume of antibiotic usage, 16 assessed adequacy of antibiotic coverage, 15 assessed CDSS uptake and use, 15 assessed cost of antibiotics, 10 assessed compliance with guidelines, and 4 assessed antimicrobial resistance. The majority of studies were conducted in the United States (45 of 81 studies).

3.3.2 CDSS interventions

The classification of CDSS interventions by Baysari and co-workers was adopted (Baysari et al., 2016). CDSS interventions found in the systematic review took four main forms: (1) stand-alone computerised decision support systems (CDSS), (2) decision support embedded within a hospital's electronic medical record (EMR) or computerized provider order entry (CPOE) system, (3) computerized antimicrobial approval systems, and (4) surveillance systems. Interventions were evaluated against usual care, no CDSS, paper-based decision support or CDSS.

3.3.3 Quality of studies

The systematic review findings indicated that the current state of evidence for CDSS in optimising antibiotic use is poor and is limited to non-Cochrane study designs. The majority of studies identified used before-and-after designs with very few including a control group. The studies included achieved an average score of (5.7 out of possible 10) on the rating scale. Random allocation of health care professionals, patients or units to a CDSS intervention was

rare. The majority of the included studies assessed an objective outcome measure (length of stay) or used subjective measures with blinded assessment.

Figure 10: PRISMA Flow Diagram

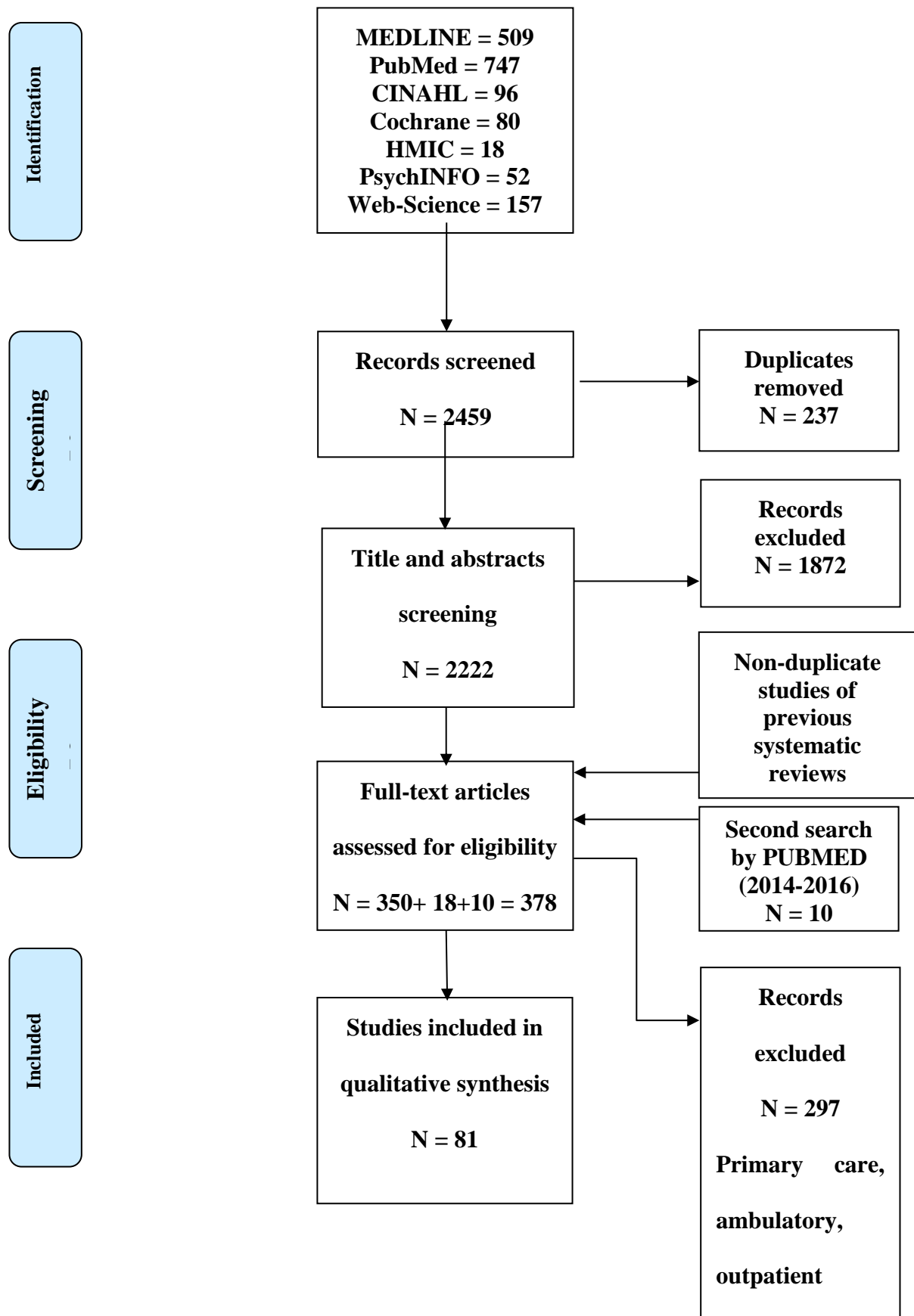


Table 16: summary table of included studies

Author, year	Quality	Setting, Country	Participants	Study design	Intervention	Primary outcome	Main findings
(Agwu et al., 2008)	8/10	175-bed tertiary children hospital, USA	199 participants	Single-site, uncontrolled before and after	Approval system	Delivery times for restricted and unrestricted antibiotics, number of dispensed restricted & unrestricted antibiotics, cost, patient complexity, length of stay	No difference in dispensing time for restricted antibiotics, but time was reduced for unrestricted antibiotics ($p < 0.001$). Cost of restricted antibiotics decreased by 21.6% (no p-value reported) but cost of unrestricted antibiotics did not change. Number of requests for approval increased post system (220 vs. 342 requests per month, no p-value reported). Number of doses of restricted antibiotics dispensed decreased by 11%. No difference in complexity or length of stay.
(Arboe et al., 2014)	4/10	Acute care hospital, Denmark	511 patients	Single-site, uncontrolled before and after	CDSS	Adequacy of antibiotic coverage, cost, length of stay and mortality	Antimicrobial coverage rates in the retrospective group for TREAT, physicians and guidelines were 65%, 51%, and 79%, respectively, and 68%, 62%, and 77%, respectively, for the prospective group; TREAT provided a significant lower coverage than local guidelines ($p < 0.001$); no differences were found in the length of stay, or hospital or 30-day mortality.
(Bourdeaux et al., 2014)	4/10	Mixed medical and surgical tertiary ICU, UK	N/A	Single-site, uncontrolled before and after	DS within CPOE/EHR	Proportion of eligible patients prescribed chlorhexidine	Proportion of eligible patients prescribed chlorhexidine increased from 55.3% to 90.4% after DS ($p < 0.001$).
Brady et al, 2014 (Brady et al., 2014)	5/10	Children hospital, USA	31 patients	Single-site ITS	DS within CPOE/EHR	Discharge on oral therapy	Increased percentage of children with osteomyelitis discharged on oral therapy from no cases (0%) to 9 cases (100%); differences in length of stay and cost were not significant.
(Buising et al., 2008a)	6/10	Teaching hospital, Australia	740 patients	Single-site, uncontrolled before-and-after, ITS	CDSS	Compliance and adequacy of empirical antibiotic prescribing	The odd ratio for concordant therapy in the academic detailing period compared to the baseline period was ($OR = 2.79 [1.88, 4.14]$, $p < 0.01$); the odd ratio for concordant therapy in the computerised decision support period compared to the academic detailing period was ($OR = 1.99 [1.07, 3.69]$, $p = 0.02$).
(Buising et al., 2008b)	5/10	365-bed referral hospital, Australia	Patients prescribed broad spectrum antibiotics	Single-site, uncontrolled before and after	Approval system	Uptake of tool, antibiotic consumption, antibiotic resistance, mortality, length of stay	Approval system uptake increased and plateaued at 250-300 new approvals per month. A fall in use of 3rd and 4th generation cephalosporins occurred ($p < 0.01$). Patterns of resistance of common pathogens remained stable. No change in mortality rate or length of stay.
(Burke and Pestotnik, 1999)	5/10	Teaching hospital, USA	11,634 patients	Single-site, uncontrolled before-and-after	CDSS	DDD/1000 patient-days, mortality, length of stay, adverse drug rate, and antimicrobial resistance patterns	Increased DDD/1000 patient-days from 226 to 299; declining ICU length of stay from 3.6 days to 2.8 days; decreased overall length of stay; decreased mortality and the incidence of adverse drug events.

(Burton et al., 1991)	8/10	Tertiary care medical centre, USA	147 patients	Single-site RCT	CDSS	Response rate, incidence of toxicity, means length of stay, length of aminoglycoside therapy, and cost	Intervention group had higher response rates (60% vs 48%); insignificant decrease in the incidence of toxicity was seen (from 9.7% to 5.1%); significant decrease in the duration of hospital stay in (from 20.3 to 16 days, $p=0.028$); potential cost savings of \$ 1311 per patient can be achieved.
(Caplinger et al., 2016)	5/10	Teaching hospital with surgical and medical intensive care units, USA	68 patients before and 59 patients after	Single-site uncontrolled before and after	CDSS	Antipseudomonal carbapenems (APC) initiations per 1000 patient-days	Aggregate monthly APC initiations decreased from 7.01 to 6.14 per 1000 patient-days after the implementation ($p=0.03$). Post-intervention APC initiations for patients with low-risk β -lactam histories decreased from 92% to 83% ($p=0.17$). No adverse events were observed in patients with low-risk β -lactam histories. The intervention was associated with a reduction in APC initiations.
(Chan et al., 2006)	5/10	ICUs of a hospital, Taiwan	762 patients (465 before and 297 after)	Single-site, uncontrolled before and after	DS within CPOE/EHR	The frequency of cases with undesirable peak ($<4\mu\text{g/ml}$) and trough ($\geq 2\mu\text{g/ml}$) serum gentamicin concentration and patient satisfaction	The frequency of gentamicin regimens that resulted in undesired levels decreased (13.5%) after implementation of the gentamicin online calculator compared to before the implementation (32.7%). The users expressed satisfaction with the dosage calculator (mean score, 4.9; $n=18-20$).
(Chan et al., 2011)	6/10	3500-bed medical centre, with 400 ICU beds, Taiwan	Patients for which restricted and non-restricted antibiotics were prescribed	Single-site, uncontrolled ITS	Approval system	Use of restricted and non restricted antibiotics, hospital infection rates, mortality rates, incidence of C. diff infection, resistance profile	Use of 3rd and 4th generation cephalosporins, fluoroquinolones & glycopeptides reduced following deployment ($p<0.001$). Use of carbapenems increased, as did some front line antibiotics ($p<0.001$). No change in hospital infection rates or mortality rates. Mixed results for resistance profiles. No change in rate of C diff.
(Chow et al., 2015) (Chow et al., 2016b)	6/10	1500-bed tertiary-care hospital, Singapore	1886 patients who were prescribed piperacillin-tazobactam or carbapenem for empiric therapy	Single-site, prospective observational cohort	CDSS	The extent to which hospitalised patients received antibiotics recommended by CDSS, 30-day all-cause mortality, the incidence of C. diff infection (CDI) and multidrug resistant organism (MDRO).	One-quarter of the 1886 patients received CDSS-recommended antibiotics. More patients treated for pneumonia (33.2%) than sepsis (12.2%) and urinary tract infections (7.1%) received CDSS-recommended antibiotic therapies. Receipt of antibiotics according to CDSS's recommendations lowered mortality risk of patients (OR 0.54, 95% CI 0.26-1.10, $p=0.09$). No effect was seen on the incidence of C. diff (OR 1.02, 95% CI 0.34-3.01), and multidrug resistant organism (OR 1.06, 95% CI 0.42-2.71).

(Chow et al., 2016a)	7/10	1500-bed tertiary care teaching centre, Singapore	All patients with electronic prescriptions of antibiotics	Single-site, three-phase cohort study	CDSS	Trend of completed launches for guidance and via auto-trigger per month, trend of proportion of accepted CDSS recommendations per month, factors associated with acceptance of CDSS recommendations	In phase 1, 23% of CDSS launches were completed which rose to 38% in phase 2 and then to 87% in phase 3. Amongst completed launches for guidance, 89% of CDSS recommendations were accepted versus 40% amongst completed launches via auto-trigger. Amongst CDSS launches for guidance, being from a medical department [adjusted odds ratio (aOR)= 1.20, 95% confidence interval (CI) 1.04-1.37] and CDSS launches during on-call (aOR=1.81, 95% CI 1.61-2.05) were independently associated with acceptance of CDSS recommendations
(Cook et al., 2011)	6/10	861-bed tertiary care teaching hospital, USA	Patients for which MRSA and C. diff culture reports were queried	Single-site, uncontrolled before and after	DS within CPOE/EHR	Use of antibiotics incidence of nosocomial infection with C. diff and MRSA, pharmacy interventions and accepted recommendations	There was a 98.1% increase in the number of antibiotic recommendations made ($p<0.0001$). There was a 28.8% decrease in use of antibiotics following intervention ($p<0.0001$). MRSA infections decreased by 45.2% ($p<0.0001$) and a 18.7% decrease in C. diff but this was non-significant.
(Cox et al., 2011)	8/10	593-bed tertiary care teaching medical centre, USA	216 patients	Single-site, uncontrolled before and after (historical control)	DS within CPOE/EHR	Appropriate aminoglycoside dosing, number of aminoglycoside orders, and peak and trough concentrations	Significant increase in adherence with reference standards (41% to 80%, $p < 0.001$); significant increase in appropriate selection of correct initial interval (63% to 87%, $p < 0.001$); significant increase of goal trough concentrations (59% to 89%, $p < 0.004$).
(Dean et al., 2015)	7/10	7 Intermountain Healthcare hospital EDs in Utah urban corridor, USA	4758 patients (2071 usual care group vs 2687 intervention group)	Multisite, controlled before and after	CDSS	30-day, all-cause mortality and patient disposition from the ED	There was no difference overall in severity-adjusted mortality between intervention and usual care EDs post-tool deployment (odds ratio OR=0.69; 95% CI 0.41 to 1.16). Patients with community acquired pneumonia experienced significantly lower mortality (OR=0.53; 95% CI 0.28 to 0.99), whereas mortality was unchanged among patients with health care-associated pneumonia (OR=1.12; 95% CI 0.45 to 2.8). Patient disposition from the ED post deployment adhered more to tool recommendations.
(Demonchy et al., 2014)	5/10	Emergency departments of three teaching centres, France	912 patients	Multisite, uncontrolled before-and-after (3 study periods after intervention)	CDSS and DS within CPOE/EHR	Compliance of antibiotics prescribed with national guidelines	Compliance of prescriptions to guidelines was improved following the use of CDSS in one ED (absolute increase +20%, $p = 0.007$); the choice of antibiotic was improved following the use of CDSS [OR = 1.94 (95% CI 1.13-3.32)].

(Devabhakthun et al., 2012)	6/10	Medical centre, USA	Patients receiving vancomycin	Single-site, uncontrolled before and after	DS within CPOE/EHR	Appropriate initial vancomycin regimens, appropriate initial trough concentrations, appropriate time of initial trough levels, appropriate number of doses administered prior to trough levels, number of levels drawn, duration of therapy	There was an increase in appropriate vancomycin doses from 40% to 56% ($p < 0.001$) but no change in the proportion with an appropriate dosing interval. The initial trough concentration was higher before the intervention than after (17mcg/ml vs. 13 mcg/ml; $p = 0.048$).
(Diasinos et al., 2015)	5/10	320-bed teaching hospital, Australia	Patients receiving gentamicin	Single-site, retrospective audit and interviews	DS within CPOE/EHR	Compliance of gentamicin prescribing (empirical cases, STAT doses and continued cases) with the Australian Therapeutic Guidelines, version 14 (2010). To determine why resources were effective or ineffective in achieving compliance to guidelines	Intravenous gentamicin was used in 545 cases, 81% of which were for short-term therapy (≤ 48 h). Of the continued dosing cases, 55% went unmonitored and the computerised dose recommendation service was rarely used. 91.4% (498/545) of subsequent empirical dosing, 72.8% (206/283) of empirical dosing interval and 44.1% (30/68) of therapeutic drug monitoring (TDM) requests were compliant with therapeutic guidelines.
(Evans et al., 1990)	8/10	520-bed private hospital, USA	Surgical patients receiving antibiotic prophylaxis	Single-site, uncontrolled before and after	Surveillance system	Cost of antibiotics, antibiotic usage	Cost of antibiotics per surgical patient decreased from \$170 to \$162 (No p-value reported). Patients received fewer doses of antibiotics following surveillance system (19 vs. 13, $p < 0.001$). 10% of patients were still receiving antibiotics 7-days post-op pre surveillance system, compared with 5% post surveillance system ($p < 0.001$).
(Evans et al., 1994)	4/10	520-bed private hospital, USA	House staff physicians prescribing antibiotics	Single-site, cross-over design	CDSS	Adequacy of antibiotic coverage, timeliness and users' perceptions	Significant increase in adequacy of antibiotic coverage (from 77% to 94%, $p < 0.001$); significant earlier prescribing of antibiotic (from 21 h to 12 h, $p < 0.035$); 88% of users recommended Antibiotic Consultant CDS and felt that it improved patient care.
(Evans et al., 1995)	4/10	12-bed shock/trauma/respiratory ICU, USA	636 patients	Single-site, uncontrolled before-and-after	CDSS	Adoption rates, adequacy of antibiotic coverage, cost, and adverse drug events	Recommendations of Antibiotic Assistant were adopted 218 (37%) times; cost of antibiotics decreased (from \$61.72 to \$50.97); insignificant decrease of adverse drug events (from 2.4% to 0.09%, $p = 0.164$).
(Evans et al., 1998)	6/10	12-bed ICU of 520-bed tertiary private hospital, USA	1681 patients	Single-site, uncontrolled before-and-after	CDSS	DDD/100 occupied bed-days, cost of hospitalisation, and cost of surveillance of adverse drug events	Significant reductions were seen in DDD/100 occupied bed-days ($p < 0.001$); significant reductions in cost of hospitalisation ($p < 0.001$) and in cost of antimicrobial agents ($p < 0.001$).

(Evans et al., 1999)	8/10	520-bed private hospital, USA	tertiary	Surgical patients receiving excessive antibiotics prophylaxis (4494 patients before and 1974 patients after)	Single-site, uncontrolled before and after	Surveillance system	Number of patients receiving excessive dosages of antibiotics, rate of adverse drug events	During the post period, 44% of patients received excessive dosages, compared to 50% in the pre period ($p<0.001$). Patients received excessive dosages for 2.9 days during post period and 4.7 days during the pre ($p<0.001$). Fewer doses of antibiotics were given post intervention, and fewer grams at less cost. 0.3% adverse drug events were found post, compared to 0.9% pre ($p<0.001$).
(Faine et al., 2015)	7/10	ED of teaching Level 1 trauma centre, USA	trauma	278 patients (100 pre- and 178 post-intervention)	Single-site, uncontrolled before-and-after	CDSS	The proportion of appropriate vancomycin doses based on actual body weight, mortality and length of stay	The dose calculation tool was associated with an increase in mean vancomycin dose ($[14.1\pm5.0]$ vs. $[16.5\pm5.7]$ mg/kg, $p<0.001$) and a 10.3% absolute improvement in first-dose appropriateness (34.4% vs. 24.0%, $p=0.07$). 28-day mortality (odds ratio OR 1.72; 95% CI $[0.76-3.88]$, $p=0.12$) was not affected.
(Filice et al., 2013)	5/10	Teaching veterans hospital, USA	veterans	500 patients	Single-site cohort study	CDSS	Appropriateness of antibiotic coverage, and mortality	CDSS courses were more likely to be appropriate (111/254, 44%) compared with non-CDSS (81/246, 33%, $p = 0.013$); CDSS courses were more likely to be appropriate than non-CDSS courses (OR= 1.83, CI, $[1.13-2.98]$; mortality was not significantly correlated with CDSS use (OR, 1.5; 95% CI, 0.6-3.5).
(Fischer et al., 2003)	5/10	Teaching hospital, USA	hospital,	Hospitalised patients receiving targeted medications	Single-site, uncontrolled before-and-after	CDSS	DDD, length of stay, case-mix index and total drug cost	Significant decrease of the intravenous DDD by 11.1% ($p=0.002$) and significant increase of the average oral DDD by 3.7% ($p = 0.002$); the average hospital length of stay and case-mix index subtly increased, while total drug cost increased by 12%.
(Garner et al., 2015)	5/10	38- bed teaching hospital, USA	NICU of hospital,	79 patients (34 patients pre- and 45 patients post-intervention)	Single-site, uncontrolled before-and-after study	DS within CPOE/EHR	Overall, prescribing and omission error rate per order	The overall error rate per order decreased from 1.7 to 0.8 ($p<0.001$) and potential error rate from 1.0 to 0.06 ($p<0.001$). The reduction in omission rate per order from 0.2 to 0.1 was not significant ($p=0.174$). The prescribing error rate per order increased from 0.4 to 0.7 ($p=0.3$).
(Giuliano et al., 2011)	4/10	2 adult ICUs, USA		135 patients	Multisite, uncontrolled before-and-after	CDSS	Adherence to the resuscitation and management sepsis bundles, and time to complete these two bundles and time to antibiotic administration	Significant improvement of adherence to resuscitation sepsis bundle ($p = 0.01$) and significant decreased time to administer antibiotics ($p = 0.006$); no significant improvement was seen for adherence to management bundle or time to complete the resuscitation or management bundles.
(Grayson et al., 2004)	4/10	430-bed teaching hospital, Australia	tertiary	Patients prescribed ceftriaxone, cefotaxime and vancomycin for which approval was sought	Single-site, Uncontrolled before and after	Approval system	Number of approved/non approved courses of ceftriaxone/ cefotaxime and vancomycin, concordance between system recommendation and use	No change in use of antibiotics. 48% of phone approvals were substituted by system approvals

(Hall et al., 2015)	8/10	ED in a tertiary care hospital, USA	597 patients (220 in the pre-CPOE and 377 in the post-CPOE group)	Single-site, uncontrolled before and after	DS within CPOE/EHR	Rate of appropriate initial ED vancomycin doses, as per hospital protocol.	Appropriate dosing of vancomycin increased by 21.9% (45.5% to 67.4%, $p < 0.05$). In critically ill patients, there was 16.3% increase in appropriate dosing with 44.7% (38/85) in the post-CPOE group compared with 28.4% (19/67) in the pre-CPOE group.
(Hamad et al., 2015)	8/10	950-bed acute NHS teaching hospital, UK	Patients receiving vancomycin and gentamicin	Single-site, uncontrolled before and after	DS within CPOE/EHR	The accuracy of vancomycin and gentamicin initial doses	Gentamicin dose errors fell from 61.5% to 44.2%, $p < 0.01$. Incorrect vancomycin loading doses fell from 58.1% to 32.4%. Incorrect vancomycin first maintenance doses fell from 55.5% to 33.1%, $p < 0.01$. Loading and first maintenance vancomycin doses were both incorrect in 37.4% of patients before and 13.4% after calculator implementation, $p < 0.01$.
(Haynes et al., 2011)	6/10	705-bed tertiary hospital for intervention and 327-bed tertiary hospital for control, USA	Eligible patients received antimicrobial surgical prophylaxis	Multisite, controlled before and after	DS within CPOE/EHR	The percentage of surgeries with timely discontinuation of antibacterial surgical prophylaxis after surgery, and post-surgical infection rate	Significant increase in timely discontinuation of antibacterial agents in the intervention group from 38.8% to 55.7% ($p < 0.001$); the prevalence of infection was 14% after the intervention implementation.
(Heininger et al., 1999)	4/10	Teaching hospital, USA	447 patients	Single-site, retrospective study	CDSS	Appropriateness of diagnosis, drug-bug match, and therapeutic choice of antibiotic	74% of the empirically prescribed antibiotics matched the antibiotic susceptibility patterns; similarly, 90% of the calculated therapy corresponded with the antibiograms.
(Helmons et al., 2010)	5/10	700-bed teaching hospital, The Netherlands	1788 patients admitted to the ICU	Single-site, retrospective study	CDSS	Dose adjustments, duration of exposure and associated costs	Dose adjustment of antimicrobials was omitted in 163 patients (86%) with moderate renal failure and 13 patients (54%) with severe renal failure. Excessive exposure was most frequently detected in patient receiving fluconazole and ciprofloxacin (median duration of 6 days). In one ICU, more than €16,000 can be saved annually by adjusting the dosage according to renal function of frequently prescribed antimicrobials.
(Hermsen et al., 2012)	7/10	624-bed acute care medical centre, USA	607 patients before and 791 patients after	Single-site, uncontrolled before and after	Surveillance system	Alerts generated, actionable alerts, proportion of alerts resulting in an intervention, proportion of recommendations accepted.	Implementation led to an increase in the number of intervention attempts (pre = no interventions documented, post = 284), but only 30% of alerts led to interventions. 88% of interventions were accepted.
(Hulgan et al., 2004)	4/10	Teaching hospital, USA	Patients for which quinolone orders, oral or intravenous, were placed.	Single-site, uncontrolled ITS	DS within CPOE/EHR	The proportion of inpatient quinolone orders placed for oral formulations before and after deployment of the intervention	There was an increment of oral quinolone orders from 4202 (56%) before the intervention to 4760 (62%) after; the time series analysis showed a significant overall 5.65% increase (95% CI 2.8-8.4%; $p < 0.001$) in weekly oral quinolone orders after deployment of the intervention.

(Hum et al., 2014)	5/10	Two NICUs affiliated with an teaching hospital, USA	452 patients who were prescribed antibiotics	Multi-centre prospective cohort and user survey	CDSS	Patterns of use of CDSS and users' acceptance and satisfaction	1,303 CDSS activations for 452 patients occurred representing 22% of patients prescribed antibiotics during this period. Most survey respondents (63%) were aware of the CDSS tool, but fewer (37%) used it during their most recent NICU rotation. Summarizing culture results (43%) and the provision of antibiotic recommendations (48%) were considered the most useful features of CDSS.
(Hwang et al., 2004)	6/10	600-bed teaching hospital, Taiwan	121 patients	Single-site, post-intervention with control	CDSS	Peak and trough levels of gentamicin	Peak levels were lower in the control group than in the intervention group (6.4 mg/l vs 6.13 mg/l, $p=0.035$) and trough concentrations were lower in the intervention group than control (0.89 mg/l vs. 1.06 mg/l, $p<0.001$).
(Karsies et al., 2014)	6/10	Tertiary care PICU, USA	Chart review of patients were reviewed one year before and after DS	Single-site, uncontrolled before and after	DS within CPOE/EHR	Risk-appropriate antibiotics, culture-appropriate antibiotics, time from culture to appropriate antibiotics	Post intervention patients were more likely to receive risk-appropriate antibiotics (15% vs. 76%, $p<0.0001$) and culture appropriate antibiotics (64% vs. 89%, $p<0.0001$). Overall, no difference in time to first antibiotics between groups ($p=0.99$) but post patients had a shorter time from culture results to appropriate antibiotics, compared to pre patients (5.9 vs. 9.6 h, $p<0.0001$).
(Kazemi et al., 2011)	4/10	Neonatal ward of 400-bed tertiary teaching hospital, Iran	Patients with antibiotic prescriptions were reviewed to identify prescribing errors	Single-site, uncontrolled before and after (three periods)	DS within CPOE/EHR	Proportion of medication errors (prescription and transcription errors)	Rate of non-intercepted errors fell from 53% during the pre-intervention period to 34% following the introduction of DS ($p<0.001$). No change in rate of errors was demonstrated with CPOE.
(Kim et al., 2013)	8/10	1950-bed tertiary care university hospital, South Korea	Medical review of patients were reviewed one year before and after DS implementation	Single-site, uncontrolled before and after	DS within CPOE/EHR	Time between culture and administration of appropriate antibiotics, length of stay and 30-day mortality	Appropriate therapy was started earlier in the intervention group compared to control (13.5 vs.20, $p=0.136$). Median length of stay decreased from 23 to 19.5 days (0.036). No change in mortality.
(King et al., 2007)	5/10	Tertiary paediatric hospital, Canada	334 patients	Single-site, uncontrolled before-and-after	DS within CPOE/EHR	The frequency of ordering of antibiotics; length of hospital stay; disease severity; trainees' perceptions	Significant reduction of patients receiving antibiotic from 35% to 22% following the introduction of a Clinical Evidence Module (CEM) (relative decrease 37%, $p = 0.016$).

(Kofoed et al., 2009)	6/10	800-bed university hospital, Denmark	161 patients	Single-site, non-interventional cohort	CDSS	Adequacy of antibiotic coverage for empirical treatment, types of antimicrobials used and cost	Adequacy of antibiotic coverage was significantly higher by CDSS than that by clinical practice (86% vs 66%, $p=0.007$). There was no significant difference in the cost of future resistance between treatments chosen by CDSS and those by physicians. There was no significant difference in the direct cost for antibiotics while there were higher costs with CDSS when including patients without antibiotic therapy. There was a significant lower cost of side effects with CDSS.
(Kweekel et al., 2004)	6/10	University hospital, Netherlands	Patients who were prescribed restricted antibiotics,	Single-site, uncontrolled before and after	DS within CPOE/EHR	Appropriate antibiotic prescribing	Percentage of correct antibiotics increased from 25% to 43.7% after implementation of DS ($p<0.001$). Errors in duration of antibiotics therapy decreased from 22% to 9.7% ($p=0.01$).
(Larsen et al., 1989)	6/10	Teaching hospital, USA	6831 patients	Single-site, uncontrolled before-and-after	DS within CPOE/EHR	Timing of antimicrobial prophylaxis, post-operative infections, proportion of pre-operative antimicrobial use	Significant improvement in rates of postoperative wound infectious complications ($p < 0.03$); significant improvement in the timeliness of preoperative antimicrobial prophylaxis ($p < 0.001$); no significant effect on the frequency of antimicrobial use per patient on the day of surgery (pre-intervention 79%, post-intervention 82%).
(Leibovici et al., 1997)	5/10	Teaching hospital, Israel	496 patients	Single-site, non-interventional comparative cohort	CDSS	Cohort: The percentage of appropriate empirical antibiotic treatments,	The recommendations of CDSS were significantly inappropriate in 50 patients (23%, $p < 0.05$) and superfluous (11%) compared to physicians' recommendations in 91 patients where it was inappropriate in 42% and superfluous in 15% of the patients.
(Leibovici et al., 2013)	8/10	Teaching hospital, Israel	1683 patients	Cluster RCT	CDSS	180-day survival rate	In the intention to treat (ITT) analysis, survival insignificantly increased from 71% in the control group to 74% in the CDS group ($p = 0.2$); in the per protocol (PP) analysis, the survival percentages significantly increased from 71% in the control to 77% in CDS group ($p = 0.04$).
(Linares et al., 2011)	4/10	Veterans medical centre, USA	Patients who had either a urine culture or a urinalysis that could trigger antibiotic use of UTI	Single-site, uncontrolled before and after	DS within CPOE/EHR	Mean number of days for patients treated for a symptomatic bacteriuria and pyuria	65% reduction in mean number of antibiotic days (6.3 vs. 2.2 days, $p<0.001$).

(Liu et al., 2008)	4/10	Tertiary care centre, Taiwan	858 patients	Single-site, cohort study	DS within CPOE/EHR	The percentage of no prophylactic antibiotic, duration of prophylactic antibiotic, and post-operative wound infection rate	In clean procedures, the percentage of no prophylactic antibiotic decreased in the long run or even reached 100% for some procedures; in clean-contaminated procedures, the duration of prophylactic antibiotic after surgery mostly reduced; the post-operative wound infection rate for clean procedures did not change significantly among the three groups (0.63 vs. 0.72 vs 0.71; $p = 0.995$).
(Manjaly et al., 2012)	4/10	Teaching hospital, UK	Patients receiving once daily IV gentamicin	Single-site, retrospective analysis	CDSS	Accuracy of dose and frequency of prescription of gentamicin, and time frame for measurement of serum levels	Reductions in prescribing errors in obese patients from 43% to 20%, and non-obese patient; errors in frequency calculation decreased from 12.8% to 4%; gentamicin doses (on average) can be given within 2.5 hours of a blood sample being taken.
(May et al., 2014)	4/10	311-bed children hospital, USA	Patients whose charts were reviewed 3 years before and 9 months after intervention	Single-site, uncontrolled before and after	DS within CPOE/EHR	Appropriateness of selection and discontinuation of antibiotics	No change in the appropriateness of antibiotic selection and discontinuation (100% vs. 100%).
(McCluggage et al., 2010)	6/10	Tertiary medical centre, USA	Patients with vancomycin orders reviewed 2 months before and 2 months after nomogram introduction	Single-site, uncontrolled before and after	DS within CPOE/EHR	Vancomycin regimen appropriateness, number of regimen changes, and number of serum vancomycin concentration	There was an increase in the appropriateness of vancomycin regimens (23.7% vs. 35.8%, $p=0.003$). No difference was found in number of regimen changes or number of concentration measured.
(McGregor et al., 2006)	8/10	Tertiary care centre, USA	4507 patients	Single-site RCT	Surveillance system	Hospital antimicrobial expenditure, mortality, length of hospitalization, and time spent managing antimicrobial utilization	Savings of \$84,194; \$37.64 per patient (hospital antimicrobial expenditures in the intervention and control groups were 285,812 and 372,006, respectively; no significance difference in mortality (3.26% vs. 2.95%, $p = 0.55$) or length of hospitalisation (3.84 vs. 3.99 days, $p = 0.38$); the antimicrobial management team spent around one hour less every day on the intervention group.
(Micek et al., 2014)	5/10	Teaching hospital, USA	3,616 patients	Single-site, cohort study	CDSS	Appropriateness of initial antibiotic treatment, hospital mortality, length of hospital stay, and survival in hospital or ICU	900 (24.2%) patients were alerted and they were significantly more likely to receive sub-optimal antibiotic therapy (7.1% vs 2.9%, $p < 0.001$); alerted patients had significantly higher hospital mortality (29.9% vs 23.6, $p < 0.001$) and hospital length of stay (median, 13.1 vs 10.7 day, $p < 0.001$) compared with non-alerted patients.

(Mullett et al., 2001)	4/10	26-bed Paediatric ICU, USA	1758 patients	Single-site, uncontrolled before-and-after	CDSS	Number of antibiotic orders placed, pharmacist intervention, and sub-therapeutic and excessive antibiotic dosage risk days	Significant reduction in the number of orders placed per anti-infective course by 11.5% ($p < 0.01$); significant reduction of the rate of pharmacist intervention (59% decrease in the rate of intervention for wrong anti-infective doses and 58% decrease in the rate of clinician requests for dosing help, $p < 0.01$); significant reduction in the rate of anti-infective sub-therapeutic (36% decrease) and excessive patient days (28% decrease), $p < 0.001$.
(Mullett et al., 2004)	5/10	Tertiary care centre, USA	506 patients	Single-site, retrospective study	CDSS	The proportion of appropriate and effective empiric antimicrobial	Empiric antimicrobial therapy suggested by CDS system was significantly more effective than empiric antimicrobial therapy suggested by physicians (86% vs. 66%, $p < 0.001$).
(Nachtigall et al., 2014)	5/10	Tertiary care centre, Germany	1316 patients	Single-site uncontrolled before-and-after	CDSS	The percentage of days with adherence guidelines, antibiotic-free days, and morality	Adherence to guideline increased from 61% before intervention to 92% in post 1, decreased in post 2 to 76% and remained significantly higher compared with baseline in post 3, with 71% ($p=0.178$); antibiotic-free days increased over study periods; at all time periods, mortality for patients with high guideline adherence was lower with 8% versus 12.3% ($p=0.014$) and an adjusted OR of 1.56 (95% CI 1.05 to 2.31).
(Paul et al., 2006)	8/10	3 university primary and tertiary care centres in Israel, Germany and Italy	Cohort study: 1203 patients; randomised trial: 2326 patients	Multisite Cohort and RCT	CDSS	Appropriateness of antibiotic treatment cost of observed side effects, duration of hospital stay, and overall 30-day mortality	Cohort: appropriate empirical antibiotic treatment was prescribed by TREAT more significantly and frequently than physicians (70% vs. 57%, $p = 0.0001$); RCT: the rate of appropriate empirical antibiotic treatment was significantly higher in intervention versus control wards [73% vs. 64%, odds ratio (OR) 1.48, CI: 0.95-2.29].
(Pestotnik et al., 1996)	5/10	Teaching hospital, USA	162,196 patients	Single site descriptive epidemiologic study.	CDSS	Timing and duration of prophylactic surgical antimicrobials, rates of ADE, patterns of antimicrobial resistance, mortality, length of stay, and DDD/100 bed -days	Increased proportion of hospitalised patients who took antibiotic from 31.8% in 1988 to 53.1% in 1994; decrease in DDD by 22.8%; improved timing of preoperative surgical prophylactic antibiotics from 40% of patients in 1988 to 99.1% in 1994; stabilisation of antimicrobial resistance patterns and length of stay; significant decrease in mortality rate from 3.65% in 1988 to 2.65% in 1994 ($p < 0.001$).

(Pogue et al., 2014)	8/10	3 hospitals, 1100-beds, USA	Patients with Gram-negative bacteraemia (189 patients before and 199 patients after)	Multisite, controlled before and after	Surveillance system	Time to appropriate therapy, length of stay, 30-day mortality	Patients in the intervention group had a lower median time to appropriate therapy than controls (p=0.02) but this was also the case in the pre period (p=0.01). Length of stay was lower in the intervention group (7 vs 8, p<0.001) but the surveillance system had no impact on mortality.
(Potasman et al., 2012)	4/10	400-bed referral hospital, Israel	Patients prescribed antibiotics for which approval is needed	Single-site, uncontrolled before and after	Approval system	Total pharmacy expenditure, expenditure of antibiotics, number of antibiotics requests, rejections by ID team, reasons for rejections	Antibiotic expenditure dropped by 17% (No p-value reported). Over 9000 requests were placed in the system in 1 year, 20.5% were rejected, 43% of those for improper indications.
(Revolinski, 2015)	6/10	Tertiary medical centre, USA	333 patients (172 historical group and 161 intervention group)	Single-centre, uncontrolled before and after	DS within CPOE/EHR	Overall guideline compliance for the treatment of CDIs, utilisation rate of the order set	Compliance with guideline was similar before and after implementation of the Best Practice Alert (BPA) despite significant increase in <i>C. difficile</i> order set utilization. Significantly more patients received metronidazole for severe infection and significantly fewer patients with severe complicated infections did not receive combination therapy.
(Roberts et al., 2010)	5/10	Teaching hospital for geriatrics, Australia	1001 patients	Single-site, uncontrolled before-and-after	CDSS	The rate of dosing conformity, and appropriateness of therapeutic drug monitoring	Improvements were seen in dosing conformity for gentamicin (63-87%, p=0.01), and vancomycin (47-77%, p=0.07); improvements were seen in therapeutic drug monitoring for gentamicin (70-90%, p=0.02) and vancomycin (61-84%, p=0.17); renally cleared medications were held during acute renal impairment on 62% of instances in the post-intervention compared with 38% pre-intervention, (p=0.01).
(Rodriguez-Maresca et al., 2014)	6/10	Third-level hospital, Spain	218 patients	Single-site, uncontrolled before-and-after	CDSS	The appropriateness of PMRTR and LRM recommendations	The percentage of appropriateness of the empiric antibiotic treatment was significantly higher when PMRTR and LRMs guidelines were adopted rather than other criteria; LRMs were used for antibiotic prescription in 20.2% of the patients and PMRTRs in 78.2%, and active antibiotics against the finally identified bacteria were prescribed in 80.0% of the former group and 82.4% of the latter.
(Rohrig et al., 2008)	8/10	14-bed surgical ICU, Germany	Patient data were extracted from EMR/CPOE	Single-site, uncontrolled before and after	DS within CPOE/EMR	Adequate antibiotic therapy, ICU mortality and length of stay	There was an increase in the adequacy of antibiotic treatment from 47.8% pre-DS to 72.5% post-DS. There was a reduction in mortality from 40.9% to 26.5% (p=0.06). No reduction in length of stay was shown.

Schulz et al, 2013 (Schulz et al., 2013)	5/10	Teaching medical centre, USA	Patients for whom best practice alert (BPA) was issued	Single-site, uncontrolled before-and-after	CDSS	The percentages of accepted, accepted with modification and rejected de-escalation recommendations	A total of 1,285 stewardship BPAs were created; of which 244 (18.9%) were created and acted upon within 72 hours as the main aim of these alerts was de-escalation; 169 BPAs (69%) were accepted, 30 (12%) were accepted with modification and 45 (18%) were rejected.
(Shojania et al., 1998)	7/10	Teaching hospital, USA	1798 patients	Single-site RCT	DS within CPOE/EHR	The frequency of initiation and renewal of vancomycin therapy and the duration of therapy prescribed	Intervention group had 32% fewer orders (11.3 versus 16.7 orders per physicians, (p = 0.04); 28% fewer patients received initiation or renewal vancomycin orders (7.4 versus 10.3 orders per physicians, p = 0.02); 36% lower duration of vancomycin therapy (26.5 versus 41.2 days, p = 0.05).
(Sintchenko et al.)	6/10	Tertiary hospital, Australia	31 infectious diseases and critical care clinicians	Multisite cross over trial	CDSS	Adoption rate, decision effectiveness, clinical impact and time to make decision	VAP guidelines were used in 24 (39%) of the 62 cases scenarios, microbiology reports in 36 (58%) and CDSS in 37 (60%); more time was required to take decision using CDS system (245 seconds) than with unguided methods (113 seconds) (p < 0.001); clinical impact scores for CDS plus laboratory reports, laboratory reports and guidelines were 0.58, 0.45 and 0.26, respectively.
(Sintchenko et al., 2005)	6/10	ICU of tertiary hospital, Australia	12 intensivists and advanced trainees	Single-site, uncontrolled before-and-after	CDSS	DDD/1000 patient-days, length of stay, and mortality	Significant decrease in patients' length of stay from 7.15 in pre-intervention period to 6.22 bed-days in post-intervention period (p = 0.02); significant reduction in DDDs per 1,000 patient-days of antibiotics (beta-lactams, vancomycin, fluoroquinolones, carbapenems and macrolides) from 1,767 DDD to 1,458 DDDs/1000 patient-days (p= 0.04).
(Staicu et al., 2016)	6/10	528-bed tertiary referral community Teaching hospital, USA	Patients for whom aztreonam was prescribed at any time during their presentation	Single-site, uncontrolled before-and-after	CDSS	Total aztreonam usage (days of therapy [DOT] per 1000 patient-days) and inappropriate aztreonam usage (DOT per 1000 patient-days)	The total DOT with aztreonam significantly decreased from 9.5 per 1,000 patient-days in the pre-intervention group to 4.4 per 1,000 patient days in the post-intervention group (p<0.0001). The number of inappropriate aztreonam DOT decreased from 4.0 per 1,000 patient days to 0.8 per 1,000 patient-days (p<0.0001)

(Stevenson et al., 2005)	5/10	Five rural hospitals, USA	240 patients	Multisite, uncontrolled before-and-after	CDSS	Agreement with all recommendations made by CDS, compliance, mortality, 30-day readmission rate, and transfer to another hospital	Agreement of all recommendations had a pooled odds ratio of 1.88 (95% CI, 1.01 to 3.56, p = 0.04), and agreement with recommended dose had a pooled odds ratio of 1.97 (95% CI, 1.04 to 3.74, P = 0.04); overall mortality, 30-day readmission rates, and transfers to another facility were not different between the baseline and intervention time period across all hospitals; compliance with complete study protocol by hospitals ranged from 0% to 71%.
(Strom et al., 2010)	5/10	Two teaching hospitals, USA	1971 patients	Multisite RCT	DS within CPOE/EHR	Prescribing TPM/SMX with warfarin	The percentage of desired responses by the clinicians was 57% (n=111); the comparable percentage in the control group was 13.5% (n=20); clinicians in the intervention group were less likely than clinicians in the control group to re-order the alert triggering drug (adjusted odd ration, 0.12; 95% CI, 0.045-0.33).
(Tafelski et al., 2010a)	3/10	61-bed ICU at 3200 community acute care university hospital, Germany	186 patients	Single-site, uncontrolled before-and-after	CDSS	The relationship between adherence to antibiotic recommendations and mortality	ICU mortality was significantly increased in low adherence group (LAG) versus high adherence group (HAG) patients (odds ratio [OR] 2.43, 95% CI 1.126, 5.243); adherence to standards increased significantly by 35% (from 52.3% pre- to 87.2% post-intervention, p < 0.05).
(Thiel et al., 2009)	7/10	1200-bed teaching medical centre, USA	Patients who are diagnosed with severe sepsis selected for review 6 months before and after implementation	Single-site, uncontrolled before and after	DS within CPOE/EHR	Appropriateness of antibiotic prescribing, hospital mortality and length of stay	Patients in the post intervention group received more appropriate antibiotics 65.5% vs. 53%, had a shorter length of stay (22.4 vs. 28.7 days, p=0.02) and had reduced hospital mortality (47.4% vs 67.4%, p=0.02).
(Thursky et al., 2006)	6/10	24-bed ICU in adult tertiary hospital, Australia	986 patients	Single-site, uncontrolled before-and-after	CDSS	Number of courses of antibiotic prescribed, DDD/100 occupied ICU bed days, antibiotic susceptibility mismatches, and system uptake	Significant reduction in proportion of patients prescribed carbapenems, third-generation cephalosporins and vancomycin (OR = 0.61, p = 0.04; OR = 0.58, p = 0.001; OR= 0.67, p = 0.05, respectively); reduction of antibiotic use (from 166 to 149 DDDs/100 ICU bed days); fewer susceptibility mismatches for initial antimicrobial treatment (OR= 0.63, p=0.02).

(Traugott et al., 2011)	5/10	604-bed acute care teaching hospital, USA	Patients who had vancomycin levels ordered (100 pre and 100 post intervention)	Single-site, uncontrolled before and after	DS within CPOE/EHR	Appropriate vancomycin levels ordered	The level of appropriateness of vancomycin levels increased after DS from 58% to 68%, $p=0.02$.
(Van Sise et al., 2012)	6/10	Teaching hospital, USA	2,273 patients	Single-site, uncontrolled before and after	DS within CPOE/EHR	Appropriateness of prophylactic antibiotic treatments (type and dose preoperatively)	Significant increase in the number of women who received adequate prophylactic antibiotic from 85.7% before the intervention to 92.6% after the intervention, $p < 0.005$; the recommended antibiotics received increased from 43.4% before the intervention to 58.31% after the intervention, $p < 0.005$.
(Vincent et al., 2009)	5/10	Teaching hospital, USA	97 patients	Single-site retrospective review study	CDSS	Time to pharmacist completion of PTD request, medication turn-around times, dose adjustment for renal dysfunction, and medication errors	29 minutes was the median time for pharmacist to complete PTD; delays were seen for the intervention group in comparison to the baseline group for median time to first dose of vancomycin and aminoglycoside (185 vs. 138 min, $p = 0.45$) and for any antibiotic (134 vs. 118 min, $p = 0.42$), respectively; significant reduction in medication errors were seen in the intervention group (5 vs. 18 errors, $p = 0.002$).
(Westphal et al., 2011)	5/10	Teaching hospital, France	Patients for whom 471 pneumonia orders were generated	Single-site, uncontrolled before-and-after	DS within CPOE/EHR	Physician adherence to locally adopted guidelines	The percentage of antibiotic orders containing at least one criterion of non-conformity to the guidelines decreased significantly from 51% pre- to 33% post-intervention ($p=0.001$); the proportion of non-conform orders for the daily dosage of antibiotics decreased significantly from 26.9% pre- to 12.2% post-intervention ($p < 0.001$).
(Yong et al., 2010)	7/10	Teaching hospital, Australia	2838 Gram-negative isolates	Single-site, uncontrolled before-and-after	CDSS	Susceptibility and resistance rate. DDD/1000 bed days, number of admissions, and length of stay.	Significant improvement in susceptibility of <i>Pseudomonas</i> to imipenem (18.3% / year, $p = 0.009$), and gentamicin (11.6% / year, $p = 0.02$); lower rates of susceptibility of <i>Enterobacteriaceae</i> to gentamicin and ciprofloxacin

CDSS: computerised decision support systems; DS: decision support; EPR: electronic patient record; EHR: electronic patient record; SMX-TMP: sulfamethoxazole-trimethoprim, ITS: interrupted time series; CPOE: computerised physician order; DDD: defined daily dose, ED: emergency department, DOT: days of therapy; LRMs, local resistance maps; PMRTRs, preliminary microbiological reports with therapeutic recommendations.

3.3.4 Outcomes of CDSS use

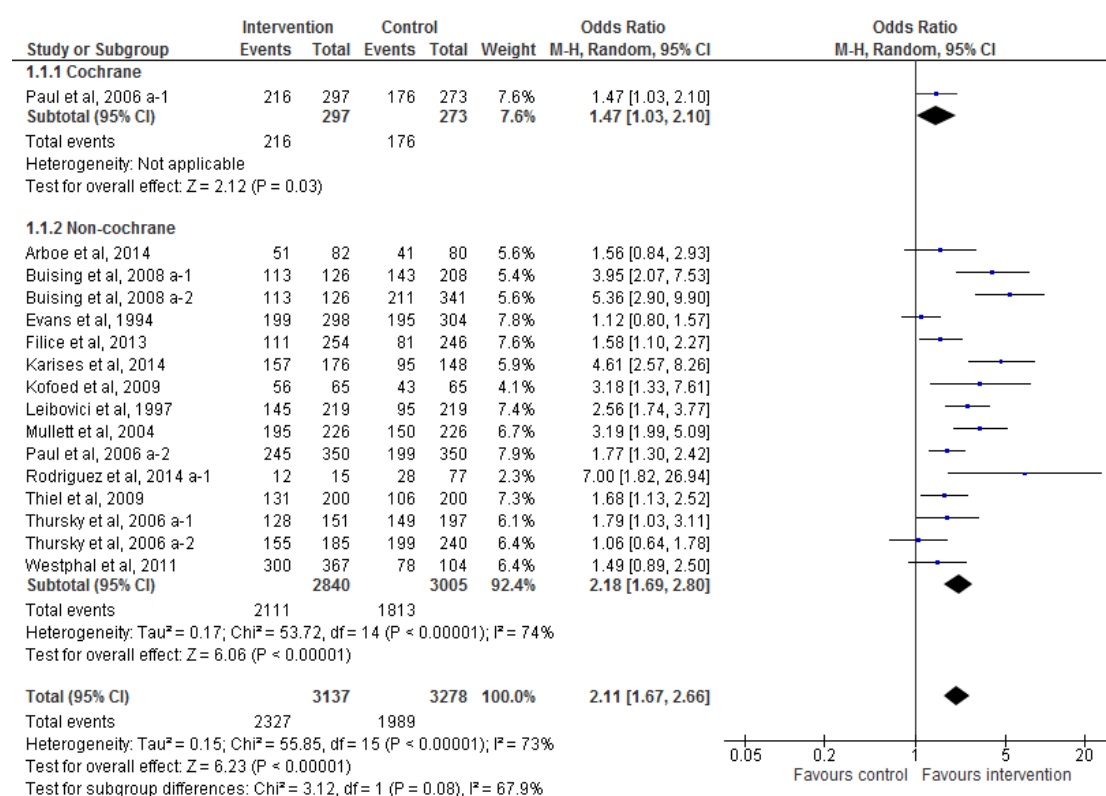
3.3.4.1 Adequacy of antibiotic coverage

Adequacy of antibiotic coverage was defined in individual studies and included retrospective review of antibiotic recommendations made by CDSS systems and measures of prescriber compliance with published guidelines when CDSS was in use. Sixteen studies reported on the adequacy of antibiotic coverage (Arboe et al., 2014, Demonchy et al., 2014, Fischer et al., 2003, Leibovici et al., 1997, Micek et al., 2014, Mullett et al., 2004, Paul et al., 2006, Rodriguez-Maresca et al., 2014, Thursky et al., 2006, Westphal et al., 2011, Evans et al., 1994, Karsies et al., 2014, Kofoed et al., 2009, Thiel et al., 2009, Filice et al., 2013, Buising et al., 2008a). Thirteen studies contained sufficient information to be included in the meta-analysis, eleven of which reported a statistically significant effect of CDSS on the adequacy of antibiotic coverage. Three studies were not included in the meta-analysis because of insufficient data to allow pooling of outcomes. Individual and pooled estimates are shown in figure 11. Overall, CDSS interventions were associated with an increase in adequacy of antibiotic coverage based on the random effects model [OR = 2.11, 95% CI, 1.67 to 2.66, $p < 0.00001$]. There was evidence of heterogeneity between studies ($\text{Chi}^2 = 55.85$, $\text{df} = 15$, $I^2 = 73\%$, $p < 0.00001$) (see figure 11)

There was evidence of an effect of CDSS interventions on the adequacy of antibiotic coverage for Cochrane compliant studies [OR = 1.47, 95% CI, 1.03 to 2.10, $p = 0.03$], and for non-Cochrane studies [OR = 2.18, 95% CI, 1.69 to 2.80, $p < 0.00001$] (see figure 11). Similarly, CDSS interventions were associated with an increase in the adequacy of antibiotic coverage for US studies [OR = 2.05, 95% CI, 1.30 to 3.24, $p = 0.002$], and for non-US studies [OR = 2.14, 95% CI, 1.61 to 2.84, $p < 0.00001$]. There was evidence of an effect of CDSS interventions on the adequacy of antibiotic coverage for hospital studies [OR = 2.04, 95% CI,

1.60 to 2.60, $p < 0.00001$], and for ICU studies [OR = 2.51, 95% CI, 1.14 to 5.51, $p = 0.02$]. A funnel plot indicates near symmetry between results (see figure in the appendix).

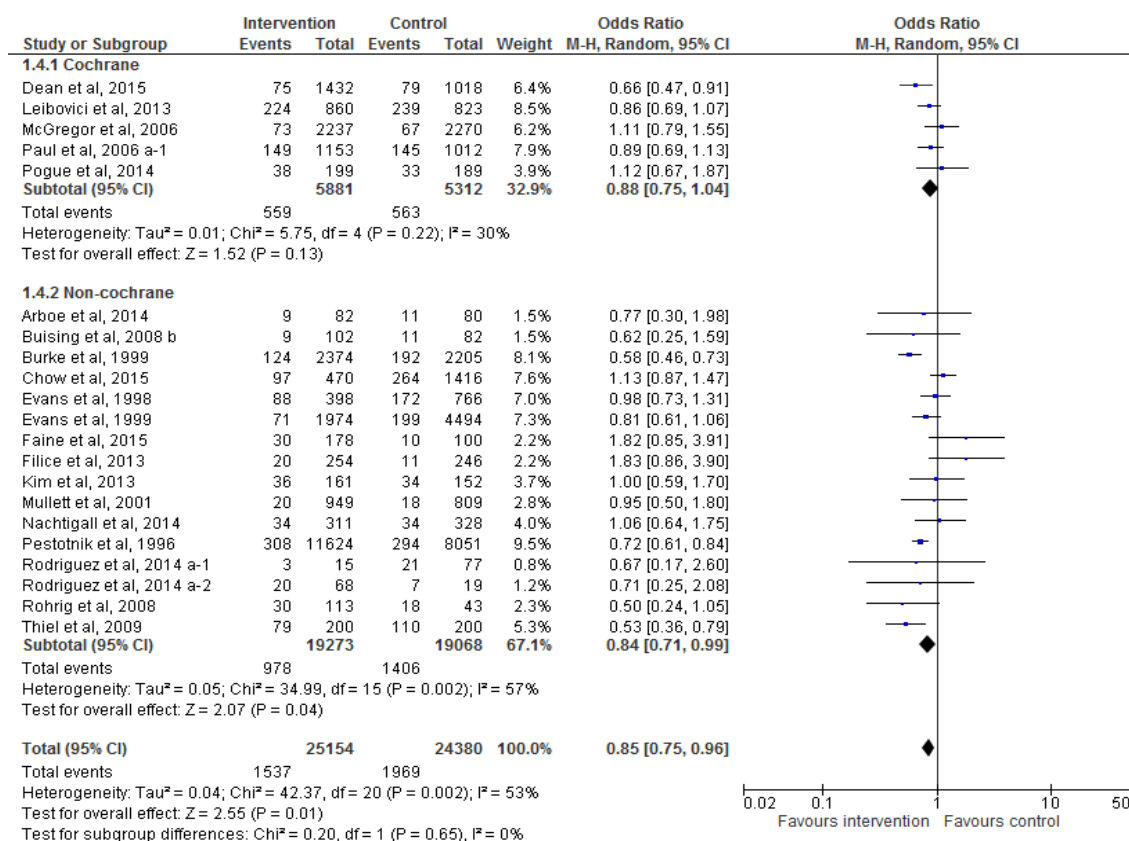
Figure 11: Forest plot from individual studies and meta-analysis for adequacy of antibiotic coverage



3.3.4.2 Mortality

Twenty-six studies evaluated the impact of CDSS on mortality (Arboe et al., 2014, Burke and Pestotnik, 1999, Evans et al., 1998, Filice et al., 2013, McGregor et al., 2006, Micek et al., 2014, Nachtigall et al., 2014, Paul et al., 2006, Pestotnik et al., 1996, Rodriguez-Maresca et al., 2014, Sintchenko et al., 2005, Stevenson et al., 2005, Tafelski et al., 2010a, Chow et al., 2016b, Dean et al., 2015, Faine et al., 2015, Kim et al., 2013, Thiel et al., 2009, Evans et al., 1999, Pogue et al., 2014, Chan et al., 2011, Leibovici et al., 2013, Buising et al., 2008b, Rohrig et al., 2008, Mullett et al., 2001). Twenty studies contained sufficient information to be included in the meta-analysis (Burke and Pestotnik, 1999, Evans et al., 1998, Filice et al., 2013, McGregor et al., 2006, Nachtigall et al., 2014, Paul et al., 2006, Pestotnik et al., 1996, Rodriguez-Maresca et al., 2014, Dean et al., 2015, Pogue et al., 2014, Chow et al., 2016b, Evans et al., 1999, Faine et al., 2015, Kim et al., 2013, Thiel et al., 2009, Arboe et al., 2014, Mullett et al., 2001, Leibovici et al., 2013, Buising et al., 2008b, Rohrig et al., 2008), four of which reported a statistically significant effect of CDSS on mortality. Six studies were not included in the meta-analysis because of insufficient data to allow pooling of outcomes. Individual and pooled estimates are shown in figure 16. Overall, results showed that CDSS interventions had a marginal statistically significant effect on mortality based on the random model. [OR = 0.85, 95% CI, 0.75 to 0.96, $p = 0.01$]. There was evidence of heterogeneity between studies ($\text{Chi}^2 = 42.37$, $\text{df} = 20$, $I^2 = 53\%$, $p = 0.01$).

Figure 12: Forest plot from individual studies and meta-analysis for mortality



There was no evidence of an effect of CDSS interventions on mortality for Cochrane compliant studies [OR = 0.88, 95% CI, 0.75 to 1.04, $p = 0.13$]. Based on non-Cochrane studies, there was a marginal statistically significant effect of CDSS interventions on mortality [OR = 0.84, 95% CI, 0.71 to 0.99, $p = 0.04$]. There was no evidence of an effect of CDSS interventions on mortality for US studies [OR = 0.84, 95% CI, 0.70 to 1.01, $p = 0.06$], or for non-US studies [OR = 0.92, 95% CI, 0.81 to 1.04, $p = 0.16$]. Similarly, there was no evidence of an effect of CDSS interventions on mortality for hospital studies [OR = 0.88, 95% CI, 0.76 to 1.01, $p = 0.08$], or for ICU studies [OR = 0.77, 95% CI, 0.59 to 1.01, $p = 0.06$].

3.3.4.3 Volume of antibiotic usage

Nineteen studies reported on the impact of CDSS on the volume of antibiotic usage (Burke and Pestotnik, 1999, Evans et al., 1998, Fischer et al., 2003, Grayson et al., 2004, Pestotnik et al., 1996, Sintchenko et al., 2005, Thursky et al., 2006, Agwu et al., 2008, Burton et al., 1991, Mullett et al., 2001, Yong et al., 2010, Shojania et al., 1998, Tafelski et al., 2010a, Cook et al., 2011, Linares et al., 2011, Staicu et al., 2016, Evans et al., 1999, Chan et al., 2011, Buising et al., 2008b). Values for total antibiotic use are summarised in table 16. Fourteen studies showed decreases in antibiotic usage (Agwu et al., 2008, Burton et al., 1991, Evans et al., 1998, Pestotnik et al., 1996, Sintchenko et al., 2005, Tafelski et al., 2010a, Thursky et al., 2006, Shojania et al., 1998, Chan et al., 2011, Cook et al., 2011, Evans et al., 1999, Linares et al., 2011, Staicu et al., 2016, Buising et al., 2008b). Two studies showed increases in antibiotic usage.(Burke and Pestotnik, 1999, Mullett et al., 2001). Burke and co-workers showed an increase in the volume of antibiotic use from 226 to 299 DDD/1000 bed days. Mullett and co-workers showed an increase in the number of doses per patient from 19.8 to 22 doses per patient. One study by Fisher and co-workers showed conflicting results as intravenous DDDs significantly decreased by 11.1% ($p=0.002$), but there was a compensatory increase in oral DDDs of 3.7% ($p=0.002$) (Fischer et al., 2003). The unit of measurement for drug use differed between studies, making it difficult to compare the impact of each intervention. The denominator was converted to 1000 bed-days where applicable. Thursky and co-workers showed a significant reduction of antibiotic DDDs (1660-1490 DDDs/1000 ICU bed-days), which was accompanied by a significant decrease in proportion of patients who received broad spectrum antibiotics (Thursky et al., 2006). Sintchenko and co-workers showed a significant reduction (-17%) of antibiotic DDDs (1925-1606 DDDs/1000 patient days) (Sintchenko et al., 2005). Evans and co-workers showed a significant reduction (-13%) of antibiotic DDDs (1852-1619 DDD/1000 patient days) (Evans et al., 1998).

Table 16: Reduction in overall antibiotic usage with CDSS interventions in secondary care

Study	Unit of measurement	Antibiotic use in non-intervention group	Antibiotic use in intervention group	Difference	P value
Agwu 2008	Doses/day	125.8 (restricted AB)	111.08	-11%	N/A
		227.5 (Unrestricted AB)	201	-12%	N/A
Buising 2008	Gradient DDD/1000 bed-days	+1.41	-0.16	-	N/A
Burke 1999	DDD/1000 pt-days	226	299	+32%	N/A
Burton 1991	DOT	8.3	7.3	-12%	0.93
Chan 2011	Gradient DDD/1000 pt-days	+0.916	+0.6437	-	N/A
Cook 2011	DDD/1000 pt-days	775.3	552.2	-28.8%	< 0.0001
Evans 1998	DDD/1000 pt-days	1852	1619	-13%	N/A
Evans 1999	DDD/1000 pt-days	1972	1882	-4.5%	N/A
Fisher 2003	DDD	N/A	N/A	-11% (IV)	0.002
		N/A	N/A	+3.7% (PO)	0.002
Grayson 2004	DDD/1000 pt-days	N/A	N/A	N/A	N/A
Linares 2011	Antibiotic days	6.3	2.2	-65%	< 0.001
Mullett 2001	Doses/patient	19.8	22	+11%	N/S
Pestotnik 1996	DDD/1000 pt-days	359	277	-23%	N/A
Shajona 1998	Antimicrobial orders/prescriber	16.7	11.3	-32%	0.04
Sintchenko 2005	DDD/1000 pt-days	1925	1606	-17%	0.04
Staicu 2016	DOT/1000 pt-days	9.5	4.4	-54%	< 0.0001
Tafelski 2010	Antimicrobial agents/day	1.5	1.3	-13%	0.05
Thursky 2006	DDD/1000 pt-days	1670	1490	-11%	N/A
Yong 2010	DDD/1000 pt-days	N/A	N/A	N/A	N/S

DDD, defined daily doses; DOT, duration of therapy; AB, antibiotics; N/A, not reported; N/S, not significant; PO, Oral; IV, intravenous.

3.3.4.4 Length of stay

Only studies that evaluated length of stay as an outcome were included in the present systematic review whereas those reporting lengths of stay as baseline characteristics of patients were excluded. Twenty-five studies reported on the impact of CDSS on ICU and/or hospital length of stay (Arboe et al., 2014, Brady et al., 2014, Burke and Pestotnik, 1999, Burton et al., 1991, Evans et al., 1998, Fischer et al., 2003, McGregor et al., 2006, Micek et al., 2014, Mullett et al., 2001, Nachtigall et al., 2014, Paul et al., 2006, Pestotnik et al., 1996, Rodriguez-Maresca et al., 2014, Sintchenko et al., 2005, King et al., 2007, Evans et al., 1995, Chow et al., 2016b, Dean et al., Kim et al., 2013, Thiel et al.,

2009, Evans et al., 1999, Pogue et al., 2014, Agwu et al., 2008, Buising et al., 2008b, Rohrig et al., 2008). Values for length of stay are summarised in table 17. Sixteen studies showed decreases in length of stay (Paul et al., 2006, Agwu et al., 2008, Burke and Pestotnik, 1999, Burton et al., 1991, McGregor et al., 2006, Pestotnik et al., 1996, Rodriguez-Maresca et al., 2014, Sintchenko et al., 2005, Evans et al., 1995, Thiel et al., 2009, Pogue et al., 2014, Kim et al., 2013, Evans et al., 1999, Chow et al., 2016b, Dean et al., 2015, Rohrig et al., 2008). Three studies showed increases in length of stay (Giuliano et al., 2011, Fischer et al., 2003, King et al., 2007). Three studies showed no change in length of stay (Brady et al., 2014, Mullett et al., 2001, Arboe et al., 2014). Three more studies reported conflicting effects of CDSS on length of stay across different intervention arms (Evans et al., 1998, Nachtigall et al., 2014). In a randomised clinical trial by McGregor and co-workers, there was no statistical difference in length of stay (3.84 vs. 3.99 days, $p = 0.38$) (McGregor et al., 2006).

Table 17: Length of stay associated with CDSS implementation

Study	Length of stay in non-intervention group	Length of stay in intervention group	Difference	P value
Agwu 2008	6.78 days	6.67 days	-1.62%	0.65
Arboe 2014	-	-	No change	N/A
Brady 2014	3.8 days	3.8 days	No change	N/S
Buising 2008	12 days (pre-1) 15 days (pre-2)	15 days (post-1) 13 days (post-2)	-	N/A
Burke 1999	10.28 days	8.84 days	-14%	N/A
Burton 1991	20.3 days	16 days	-21%	0.028
Chow 2015	9.6	8.1	-15.6	N/A
Dean 2015	3.1 days (baseline) 3.0 days (second period)	3.0 days (baseline) 2.9 days (second period)	-3.3% -3.3%	N/A
Evans 1995	6.2 days	5.8 days	-6.5%	N/S
Evans 1998	12.9 days 12.9 days	10 days (CDS followed) 16.7 days (CDS overridden)	-22.5% +29.5%	0.001
Evans 1999	8.5 days	7.9 days	-7%	N/A
Giuliano 2011	15.7 days	17.8 days	+13%	0.58
Fisher 2003	N/A	N/A	+1.9%	N/A
Kim 2013	23 days	19.5 days	-15.2 %	0.036
King 2007	2.8 days	2.9 days	+3.45%	0.125

Study	Length of stay in non-intervention group	Length of stay in intervention group	Difference	P value
McGregor 2006	3.99 days	3.84 days	-3.75%	0.38
Mullett 2001	N/A	N/A	No change	N/A
Nachtigall 2014	9.2 days	9.1 days (post-1) 9.9 days (post-2) 11.3 days (post-3)	-1% +7.6% +22.8%	<0.01
Paul 2006	9.45 days	8.83 days	-6.5%	0.055
Pestotnik 1996	7.5 days	7.3 days	-2.7%	N/A
Pogue 2014	8 days	7 days	-12.5%	< 0.001
Rodriguez 2014	19.5 days	13.8 days (LRMs)	-29%	0.156
	20.1 days	19.7 days (PMRTRs)	-2%	0.943
Rohrig 2008	15.6 days	11.25 days	-27.9	N/A
Sintchenko 2005	7.15 days	6.22 days	-13%	0.02
Thiel 2009	28.7 days	22.4 days	-22%	0.02

LRMs, local resistance maps; PMRTRs, preliminary microbiological reports with therapeutic recommendations; N/A, not reported; N/A, not stated

3.3.4.5 Cost of antibiotics

Fifteen studies reported on the impact of CDSS on antibiotics cost (Agwu et al., 2008, Arboe et al., 2014, Evans et al., 1998, Fischer et al., 2003, McGregor et al., 2006, Mullett et al., 2001, Paul et al., 2006, Buising et al., 2008a, Pestotnik et al., 1996, Shojania et al., 1998, Evans et al., 1994, Evans et al., 1995, Kofoed et al., 2009, Evans et al., 1999, Potasman et al., 2012). Values for costs of antibiotic use are summarised in table 18. The unit of cost report varied making it difficult to measure the overall impact of CDSS. Nine studies showed decreases in costs of antimicrobials after implementing CDSS (Paul et al., 2006, McGregor et al., 2006, Pestotnik et al., 1996, Agwu et al., 2008, Evans et al., 1994, Mullett et al., 2001, Evans et al., 1995, Evans et al., 1999). Four studies showed increases in costs of antibiotics following CDSS implementation (Arboe et al., 2014, Fischer et al., 2003, Mullett et al., 2001, Buising et al., 2008a). Two studies reported conflicting results on antibiotic costs (Evans et al., 1998, Buising et al., 2008a). In one study conducted by Evans and co-workers, the cost of antibiotics per patient decreased when CDSS recommendations were adopted (\$340 vs. \$102) (Evans et al., 1998). In contrast, the cost of antibiotics per patient increased when CDSS recommendations were overridden (\$340 vs. \$427) (Evans et al., 1998). Buising and co-workers showed that CDSS was superior to baseline and inferior to academic detailing in cost saving (Buising et al., 2008a). However,

Paul and co-workers reported no difference in antibiotic costs associated with observed side effects between CDSS and control groups. No study reported on the overall costs of implementation of CDSS.

Table 18: Antibiotic cost reductions associated with CDSS interventions

Study	Unit measurement of	Antibiotic cost in non-intervention group	Antibiotic cost in intervention group	Difference	P value
Agwu 2008	N/A	N/A	N/A	-21.6%	N/A
Arboe 2014	N/A	N/A	N/A	Increased	N/A
Buising 2008	Cost of antibiotics per patient	\$72.07 (baseline) \$94.47(academic detailing)	\$84.04	+16.6% -11.04%	N/A
Evans 1994	Cost of antibiotics per day	\$51.93	\$41.08	-21%	<0.001
Evans 1995	Cost of antibiotic per patient	\$382.68	\$295.65	-23%	N/A
Evans 1998	Cost of antibiotics per patient	\$340	\$102 (followed CDS) \$427(overridden CDS)	-70% +26%	<0.001
Evans 1999	Average cost of antibiotics	\$128	\$98.06	-23.4%	< 0.004
Fisher 2003	N/A	N/A	N/A	+12%	N/A
Kofoed 2009	Total cost of antibiotics per patient in Euro	€469	€482	+2.8%	0.77
McGregor 2006	Total cost of antimicrobials	\$370,006	\$285,812	-23%	N/A
Mullett 2001	Cost of antibiotic per patient	\$274.79	\$289.60	+5%	NS
Paul 2006	Total cost of antibiotic in Euro	€623.2	€565.4	-9%	0.007
Pestotnik 1996	Antibiotic cost per patient	\$122.66	\$51.90	-58%	-
Potasman 2012	Total antibiotic expenditure	4.1 million NIS	3.4 million NIS	-17%	N/A
Shajona 1998	Annual cost of antibiotics	N/A	N/A	\$90,000/year	N/A

N/A not reported, N/S not significant

3.3.4.6 Compliance to guidelines

Ten studies reported on the impact of CDSS on compliance with guidelines (Demonchy et al., 2014, Giuliano et al., 2011, Grayson et al., 2004, Nachtigall et al., 2014, Karsies et al., 2014, Revolinski, 2015, Tafelski et al., 2010b, Van Sise et al., 2012, Buising et al., 2008a, Diasinos et al., 2015). Values for the percentage of compliance with guidelines are summarised in table 19. CDSS effects were measured as absolute percentage differences between CDSS and intervention groups. All studies demonstrated that CDSS improved adherence to guidelines (see table 19). Guiliano and co-workers

showed that CDSS improved adherence to sepsis resuscitation and management care bundles (Giuliano et al., 2011). Tafelski and co-workers showed that ICU mortality was significantly increased in the low adherence group (LAG) compared to the high adherence group (HAG) (OR = 2.43, 95% CI 1.126 to 5.243) (Tafelski et al., 2010a).

Table 19: Compliance associated with CDSS interventions

Study	Compliance in non-intervention group	Compliance in intervention group	Difference	P value
Buising 2008	65% (baseline)	85% (CDS)	+20%	0.05
	75% (academic detailing)	85% (CDS); OR = 1.99 [1.07, 3.69], p = 0.02).	+10%	0.05
Demonchy 2014	26.5%	32% (post DS)	+5.5%	N/A
	34%	43.5% (post CDS)	+9.5%	
Guiliano 2011	57.6% (resuscitation bundles)	68.2%	+10.6	0.003
	84.5% (management bundles)	86.8%	+2.3%	0.48
Karsies 2014	15%	76%	+61%	
Nachtigall 2014	61.4%	92% (post-1)	+30.6%	<0.001
		76.3% (post-2)	+14.9%	<0.001
		71.1% (post-3)	+9.7%	0.001
Revolinski 2015	69.7%	71.2%	+1.5%	0.605
Tafelski 2010	39.8%	90.8%	51 %	<0.05
Van Sise 2012	85.7%	92.6%	+6.9%	<0.005
Westphal 2011	49%	67%	+18%	<0.001
Grayson 2004	N/A	76%	N/A	N/A

N/A, not reported; CDS, clinical decision support

3.3.4.7 Antimicrobial resistance

Four studies reported on AMR (Pestotnik et al., 1996, Yong et al., 2010, Chan et al., 2011, Buising et al., 2008b). In a study by Chan and co-workers, the incidence of methicillin resistant *Staphylococcus aureus* (MRSA) decreased from 65-70% before the implementation of the antimicrobial approval system to less than 60% in 2009 (Chan et al., 2011). Buising and co-workers showed a trend towards increased susceptibility of *S. aureus* to methicillin and increasing susceptibility of *Pseudomonas* spp. isolates to both carbapenems and aminoglycosides particularly after the antimicrobial approval system was introduced (Buising et al., 2008b). More research is required to reach firm conclusions of the impact of CDSS on AMR.

3.3.4.8 Use and implementation

Fifteen studies assessed aspects of the use and implementation of CDSS, such as user satisfaction (Agwu et al., 2008, Evans et al., 1998, Chan et al., 2006, Hum et al., 2014, King et al., 2007, Schulz et al., 2013), user uptake (Sintchenko et al., 2005, Hum et al., 2014, Evans et al., 1995, Buising et al., 2008b), and acceptance of CDSS recommendations (Grayson et al., 2004, Mullett et al., 2001, Stevenson et al., 2005, Chan et al., 2011, Chow et al., 2016a, Sintchenko et al., Evans et al., 1995). Buising and co-workers showed that the approval system uptake increased between 2005 and 2006 and reached a plateau of 250-300 new approvals per month (Buising et al., 2008b). Agwu and co-workers showed that user satisfaction with the antimicrobial approval system increased from 22% to 68% and from 13% to 69% among prescribers and pharmacists. Stevenson and co-workers showed that agreement with CDSS recommendations had a pooled odds ratio (1.88, 95% CI, 1.01-3.56, $p=0.04$) (Stevenson et al., 2005). In contrast, six studies showed poor user uptake of CDSS recommendations. In a study by Hum and co-workers, 37% of users used CDSS during neonatal intensive care unit (NICU) rotations (Hum et al., 2014). Sintchenko and co-workers showed low level of CDSS adoption as one-third of CDSS recommendations were accepted (Sintchenko et al.). A study by Evans and co-workers showed that 37% of CDSS recommendations were accepted. More qualitative work is needed to reach a firm conclusion on CDSS uptake.

3.4 Discussion

3.4.1 Main findings

Evidence for the impact of CDSS on antibiotic use in hospital inpatient settings has been reviewed systematically. Almost half of the studies included in the present systematic review did not appear in previous systematic reviews. This indicates the pace of the introduction and evaluation of health information technology in hospital settings. Therefore, this systematic review augments previous evidence including studies that have never been evaluated before.

The majority of studies included in the systematic review showed that CDSS interventions are associated with improvement in appropriate use of antibiotics in hospitals. Some of the included studies showed no effect of improvement. Studies were extremely variable in the types of CDSS interventions and in the outcomes assessed. The most commonly assessed outcomes were mortality, length of stay, volume of antibiotic use and adequacy of antibiotic coverage. Other outcomes assessed included system uptake, antimicrobial resistance, cost and compliance with guidelines. Only a small number of studies of this systematic review assessed health outcomes (mortality and adequacy of antibiotic coverage) which may limit the strength of evidence needed to reflect on CDSS design, selection and implementation.

The principal findings of the present meta-analysis indicate that CDSS interventions were associated with improvements in adequacy of antibiotic coverage (by more than 100%) and patient mortality (reducing the risk of death by about 15%). However, these findings were likely to be driven by data from poor quality studies. Increases in compliance with guidelines have been noted in the present review. Drawing conclusions about the effects of CDSS on length of stay and cost of antibiotics is difficult since results from the present review are conflicting. A meta-analysis by Baysari and co-workers showed similar findings of the impact of CDSS interventions on adequacy of antibiotic coverage (pooled RR: 1.19, 95% 1.06 to 1.33), on mortality (pooled RR: 0.91, 95% CI: 0.82 to 1.00, $p=0.07$), on compliance with guidelines (pooled RR: 1.92, 95% 1.25-2.95), and on length of stay (pooled mean difference: -0.84, 95%CI: -2.43 to 0.76, $p=0.30$ from random effects model) (Baysari et al., 2016). The present systematic review indicated conflicting results on CDSS uptake as some studies showed improved uptake while other showed poor adoption.

3.4.2 Strengths

This systematic review provides a comprehensive, up-to-date overview of CDSS interventions aimed at optimising antibiotic use in the hospital inpatient setting. A wide range of outcome measures were assessed including outcomes that have not been evaluated before such as cost, system uptake and

antimicrobial resistance. It is noteworthy that non-randomised designs have been commonly utilised in evaluations of health informatics developments evidenced by this systematic review. The present review included studies that were excluded by other systematic reviews including studies that failed to include a comparison group (i.e. a group that was not given access to a CDSS intervention) and studies where CDSS interventions was evaluated against non-CDSS interventions.

Given that the quality and study design of included studies were generally poor and the heterogeneity in respect of study quality and end points, the synthesis of the included studies was problematic. However, the present study was successful in conducting meta-analysis and subgroup analysis which adds to the strength of this review.

3.4.3 Limitations and future research

The present systematic review is limited by the quality of studies included for analysis coupled with limitations inherent in the applied methods. All studies were eligible for inclusion in the meta-analysis but information contained in studies enabled us to conduct meta-analysis for two outcomes: adequacy of antibiotic coverage (n=13 studies) and mortality (n=20 studies). The number of studies that reported other outcome measures (e.g. volume of antibiotic use and cost) in a uniform way was not sufficient for other meta-analyses to be conducted.

Heterogeneity in study designs, CDSS interventions, outcomes, implementation and contextual factors makes it difficult to reach firm conclusions about the impact of CDSS. Subgroup analysis was not successful in explaining or even reducing heterogeneity across subgroups. This indicates that heterogeneity was inherent in poor methodological and intervention designs.

There is a possibility that selective reporting may reduce the validity of some of the conclusions. A marginal reduction of mortality is a key finding from this systematic review; however, this finding is based on a limited number of studies (n=20). Selective reporting is beyond the control of the present study as it is unclear how many studies finding an increase in mortality would be required to nullify or reverse the current findings. It is not possible to indicate that there is no risk of increase in mortality.

Caution needs to be applied with regards to publication bias. It should be clear that an external evaluation should be reported using accepted mixed method research. There is a dearth of literature about the impact CPOE without explicit CDSS from commercial vendors which risks publication bias. Some CPOE included order sets which are of questionable decision support as they are driven by initial inappropriate indications.

Future work should include conducting high quality systematic multi-site comparative studies of different CDSS interventions for antibiotic prescribing. More qualitative work is required to highlight the barriers and facilitators of adopting CDSS technology and better understand users' perceptions and attitudes towards CDSS interventions to trigger high adoption and uptake by providers.

3.5 Conclusion

This review showed that CDSS interventions can be effective in optimising antibiotic use in hospitals. The findings of this review can be used to enrich the debate around the impact of CDSS on antibiotic optimisation. This review demonstrates the efficacy of CDSS in optimising the adequacy of antibiotic coverage across different settings. However, evidence on the effect of CDSS on clinical outcomes, economic outcomes and volume of antibiotic use was limited. CDSS appears to be safe because the present review has not shown any significant risks such as worsening mortality or length of stay. CDSS presents a promising future for optimising antibiotic use and improving patient care. However, in order to reach firm conclusions about the impact of CDSS on antibiotic use, more high-quality studies are needed within different settings and in different health systems

Table 20: Summary table

What was already known on the topic
<ul style="list-style-type: none"> • Antibiotic use in hospitals is often suboptimal. • Computerised decision support system (CDSS) interventions present a promising solution to optimise antibiotic prescribing

What this study added to our knowledge
<ul style="list-style-type: none"> • Evidence shows that CDSS interventions can be effective in improving the adequacy of antibiotic coverage and compliance with guidelines, although higher quality studies are needed to confirm such a conclusion • Evidence of the effect of CDSS interventions on mortality is marginal • Uptake of CDSS intervention is variable and needs to be addressed more thoroughly

Chapter 4: Exploring the perceptions and attitudes of health care professionals towards computerised clinical decision support: an online questionnaire

4.1 Introduction

Computerised decision support systems (CDSS) that deliver evidence-based recommendations regarding appropriate selection and use of antibiotics at the point of care have been shown to improve antibiotic prescribing. CDSS can optimise antibiotic prescribing by enforcing formulary selection and highlighting drug-drug interactions. Healthcare professionals' adoption of these systems is paramount for their success; however, acceptance of their recommendations has remained low (Sintchenko et al., 2004, Curtis et al., 2017).

Development and deployment of CDSS requires huge financial and human resources. Failure of CDSS deployment is not uncommon. Few studies highlighted the reasons for such failure. In one qualitative interview study examining a chronic disease management CDSS, the poor workflow integration and negative perceptions were the reasons why CDSS failed (Zaidi and Marriott, 2012). Many studies showed poor user uptake of CDSS recommendations. A study by Sintchenko and co-workers showed low level of adoption as one-third of CDSS recommendations were adopted (Sintchenko, et al., 2006). Another study by Evans and co-workers showed that 37% of CDSS recommendations were accepted (Evans, et al, 1998). A study by Demonchy and co-workers (Demonchy et al., 2014), has highlighted uptake and implementation issues of CDSS as a major barrier. The impact of CDSS interventions would have been greater if used regularly by prescribers. Therefore, studying human perceptions and attitudes is important in order to enhance the successful implementation of these systems

As in other countries, there is a growing interest in adopting CDSS in healthcare practice in the United Kingdom. Studies examining the perceptions and attitudes of clinicians to highlight the barriers and facilitators for system adoption. This questionnaire is an online, self-completion questionnaire designed to describe medical and non-medical healthcare professionals' perceptions and attitudes

towards an antibiotic CDSS tool under development in order to provide an insight into the determinants of its success and uptake.

The questionnaire was designed by considering the issues involved and then the issues were grouped into topics and closed and open questions were created to address these topics. The questionnaire was designed to highlight issues related to the adoption of computerised decision support, design features that would maximise uptake, and the way clinical knowledge and patient information is retrieved, integrated and intelligently filtered and presented at the point of care. The target group for the questionnaire was health care professionals working at the UHBFT.

The main objectives of this study were:

- Obtain baseline data on medical and non-medical healthcare professionals at UHBFT about the perceptions and attitudes towards CDSS.
- Explore health care professionals' awareness and previous use of CDSS.
- Explore the perceived benefits of CDSS.
- Explore healthcare professionals' clinical information needs.
- Explore healthcare professionals' perceived preferred features of CDSS.

4.2 Design, piloting and analysis

The questionnaire in the present project was designed by conceptualizing the issues to be addressed by the questionnaire. Gaps in research literature that had not been addressed by previous systematic reviews and researchers' knowledge were utilised to inform the core content of the questionnaire. These topics were clustered into domains and questions were constructed to address these issues.

The questionnaire consisted of ten questions uploaded on SurveyMonkey software and sent to respondents via e-mail. The questionnaire covered five domains ranging from information about

health care professionals' job grade (1 question), their perception towards CDSS technology (4 questions), their familiarity with Patient Information and Communication System (PICS) capabilities (2 questions), their clinical information needs (1 question) and their preferences of the design and structure of the computerised decision support (2 questions). Seven questions were closed-ended and three questions were open-ended. The questionnaire was piloted among a group of pharmacists who filled in the questionnaire in the early phases of the questionnaire development. A copy of the questionnaire is included in the appendix.

The questionnaire was sent electronically to all prescribers which comprised of 1997 senior and junior, medical and non-medical independent prescribers (pharmacists and nursing staff) working at the Trust. The questionnaire was sent to respondents via e-mail in April 2015. It was piloted with a group of pharmacists (pharmacists of the electronic prescribing team at UHBFT). A second reminder was sent eight weeks later to all recipients. No ethical approval was required for this work package.

4.3 Questionnaire population

The population surveyed was health care professionals using the PICS system at UHBFT. They consisted of consultants, speciality registrars, foundation year 1 (FY1) medical staff, foundation year 2 (FY2) medical staff, others such as pharmacists and nurses.

4.4 Data management

Questionnaire was coded by giving Yes answers the code 1, No answers the code 2, and Don't know answers the code 3. Likert scale questions were coded with codes from 1-5. Clinical information needs question was coded from 1-4. Perceived benefits of CDSS question was coded from 1-5. Preferred perceived benefits of CDSS was coded from 1-6. The coded results were put into the Statistical Package for the Social Sciences (SPSS for Windows, Chicago: SPSS Inc.). Following input

of all data, the dataset was checked for potential data entry errors by the researcher by screening questions and their corresponding codes entered.

4.5 Statistical analysis

Statistical analysis was conducted using SPSS (SPSS for Windows, Chicago: SPSS Inc.). Descriptive analysis was conducted on the data collected using Excel and SPSS. Parametric and non-parametric statistical tests were applied with the Mann Whitney test and the Student's t-test to determine any statistical differences between the variables. A p-value of ≤ 0.05 was regarded as indicative statistical significance.

4.6 Results

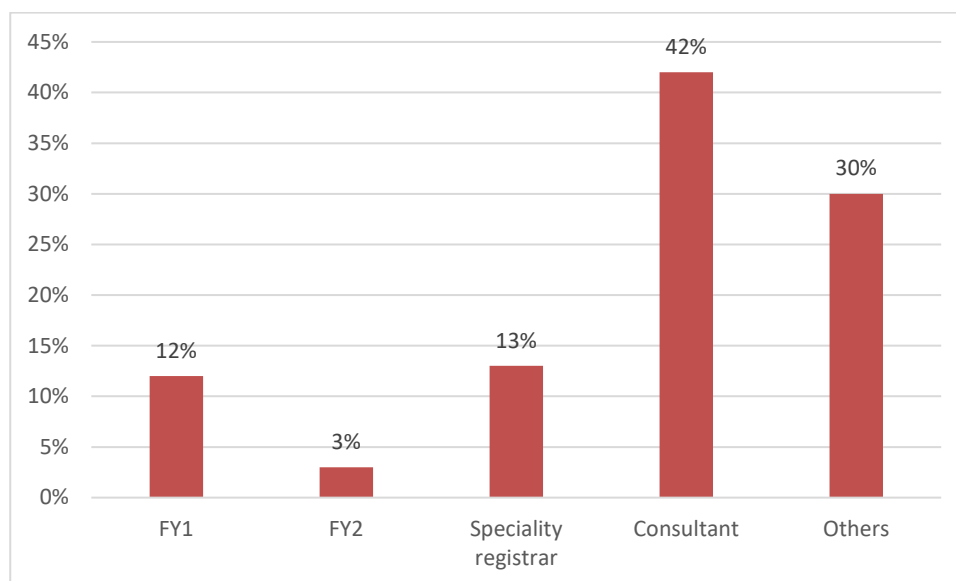
4.6.1 Response rate

A total of 122 survey responses were returned (senior medical (42%); junior medical (28 %); and non-medical (30 %). There was an overall response rate of 6.1% (122/1997).

4.6.2 Nature of the respondents

Of 122 responses, most were completed by Consultants (42%, n=51), followed by non-medical (30%, n=37), speciality registrars (13%, n=16), FY1 (12%, n=14), FY2 (3%, n=4). No participants failed to answer this question.

Figure 13: Job grade of participants and frequency of response



4.6.3 Awareness of computerised decision support system

To the question “*Are you aware that computer-aided clinical decision support systems can be used to facilitate prescribing?*”, 85% (n=103) of respondents answered “*Yes*”, 13% (n=16) answered “*No*”, 1.7% (n=2) answered “*Don’t know*”. 104 respondents experienced the awareness of the impact of CDSS on optimising prescribing. The question was answered by 121 participants, one participant omitted it.

4.6.4 Previous experience with CDSS

To the question “*Have you previously used a computer-aided clinical decision support system?*” 50.4% (n=61) answered “*Yes*”, 45.5% (n=51) answered “*No*”, 4.1% (n=5) answered “*Don’t know*”. Almost half of participants have had previous experience with CDSS in prescribing medicines. The question was answered by 121 participants, only one participant did not answer the question.

4.6.5 Awareness of PICS decision support functionality to support evidence based practice

When asked “*Are you aware that the PICS system is capable of providing computerised clinical decision support functionality in order to support evidence-based practice?*” 78.3% (n=94) answered “*Yes*”, 19.2% (n= 23) answered “*No*”, 2.5% (n=3) answered “*Don’t know*”. The question was answered by 120 participants, only 2 participants did not answer the question.

4.6.6 Acknowledgment of IT role in improving antibiotic prescribing

When asked to describe the level of agreement with the following sentence “*The use of information technology will improve antibiotic prescribing at UHBFT*”, 0.8% (n=1) answered “*Strongly Disagree*”, 1.7% (n=2) answered “*Disagree*”, 10.1% (n=12) answered “*Neither agree or disagree*”, 57.1% (n=68) answered “*Agree*”, 30.3% (n=36) answered “*Strongly agree*”. The question was answered by 119 participants, only 3 participants did not answer the question.

4.6.7 Acknowledgment of the value of CDSS to optimise antibiotic use

When asked to acknowledge the value of CDSS to optimise antibiotic use, 0.8% (n=1) answered “*Strongly disagree*”, 0.8% (n=1) answered “*disagree*”, 5.1% (n=6) answered “*Neither agree nor disagree*”, 65.3% (n=77) answered “*Agree*” and 28% (n=33) answered “*Strongly agree*”. The question was answered by 118 participants, only 4 participants failed to answer this question.

4.6.8 Level of agreement of how good antimicrobial prescribing at UHBFT is

When asked to check the level of agreement with this statement “*antimicrobial prescribing at UHBFT is already as good as it can be*”, 13.6% (n=16) answered “*Strongly disagree*”, 66.1% (n=78) answered “*Disagree*”, 19.5% (n=23) answered “*neither agree nor disagree*”, 0.8% (n=1) answered “*Agree*” and nobody answered “*strongly agree*”. The question was answered by 118 participants, 4 participants did not answer the question.

4.6.9 Perceived benefits of CDSS

When asked to select from a list of the perceived benefits of CDSS, 82.6% (n=95) answered “*De-escalation of antibiotic therapy*”, 92.2% (n=106) answered “*Suggesting an antibiotic therapeutic regimen*”, 48.8% (n=56) answered “*Monitoring antibiotic side effects*”, 76.5% (n=88) answered “*Therapeutic drug monitoring*” and 70.4% (n=81) answered “*Monitoring of antibiotic drug interactions*”. The question was answered by 115 participants; 7 participants did not answer the question.

4.6.10 Clinical information needs

When asked about the most required clinical information needs of prescribers, 115 answered the question and 7 did not. 83.5% (n=96) answered “*glomerular filtration rate (GFR)*”, 92.2% (n=106) answered “*Allergy status*”, 65.2% (n=75) answered “*Weight*”, 96.5% (n=111) answered “*Microbiology sensitivity results*”. The question was answered by 115 participants, only 7 participants did not answer the question.

4.6.11 Perceived preferred features of CDSS

When asked about perceived preferred features of CDSS, 114 participants answered the question and eight did not answer. 80.7% (n=92) answered “*Disease specific guidelines*”, 54.4% (n=62) answered “*Comparable speed with PICS*”, 74.6% (n=85) answered “*Ability to be updated to reflect changes*”, 57.9% (n=66) answered “*Ability to default antibiotic course of length*”, 68.4% (n=78) answered “*Alert generation*”, and 81.6% (n=93) answered “*Ability to suggest an antibiotic regimen*”.

4.6.12 General comments on CDSS

Participants left several comments to questions 8,9 and 10. To question number 8 ‘*what are the perceived benefits of CDSS?*’, one participant suggested a default stop date for antibiotic use in order to reduce to the risk of allergic reactions. Another participant recommended a default length of

antibiotic course. Flagging up previous antibiotic use was also recommended as was the value of annotating the indication for antibiotic use.

To question number 9 '*what are your clinical information needs?*', some participants left comments. One participant recommended previous antibiotic use as one of the clinical information needs. Other recommended that Trust guidelines and diagnostic criteria should be available on PICS. It was also thought that the patient clinical status, severity of illness, temperature and CPR flowsheets should be available on the prescribing system.

Comments were left in response to question number 10 '*what are the preferred perceived features of CDSS?*'. One participant recommended the automatic adjustment of antibiotic doses in renally impaired patients. It was also recommended that CDSS to be as fast as the PICS system. Displaying a link of Trust guidelines on PICS for empirical infections was also recommended as was the option to overrule CDSS recommendations.

4.7 Discussion

4.7.1 Main findings

The questionnaire had a low response of 6.1% that reflects low external validity. External validity is the extent to which the result of a research study can be generalised to other situations and other people (Steckler and McLeroy, 2008). The majority of participants showed positive attitudes and perceptions towards the potential benefits of implementing CDSS. Also, the majority of participants showed a high level of awareness of CDSS especially among senior doctors. That is of interest as senior doctors were making many of the prescribing decisions and their negative perceptions towards CDSS could have influenced junior prescribers' perceptions. Evidence shows that senior prescribers' perceptions and attitudes have been shown to affect successful implementation of CDSS. In a study

by Zaidi and co-workers, senior prescribers scored higher on barriers to adopt CDSS than junior prescribers (Zaidi and Marriott, 2012). This was of interest as senior prescribers were asked to state what they thought were the barriers that their junior prescribers encountered while using the system. It has been shown that senior prescribers and opinion leaders have an influence on the success of implementing CDSS. In a study by Stevenson and co-workers, it was found that resistance from senior prescribers hindered the successful implementation of antibiotic CDSS (Stevenson et al., 2005).

Almost half of respondents had not used or heard of CDSS before and this could explain some of the negative or even neutral perceptions and attitudes when answering the questionnaire. In a survey in England showing how many Trusts have adopted electronic prescribing, only 7% had fully implemented electronic prescribing with clinical decision support functionalities (Cresswell et al., 2013).

Also, it was notable in the present study that senior prescribers expressed a high level of awareness of CDSS and its role in improving antibiotic prescribing and prescribing decision in line with evidence-based practice.

The majority of participants acknowledged that prescribing of antibiotics is not as good as it could be. This is important, as it provides a driver for embracing information technology as a tool for improving antimicrobial stewardship. Information technology and the use of CDSS has been advocated as a strategy to improve antimicrobial prescribing and successfully apply antimicrobial stewardship.

Because of the nature of the work of senior prescribers and the fact they spend less time in direct contact with patients compared to junior prescribers and pharmacists, they have different perceived benefits of CDSS and different clinical information needs. Microbiology sensitivity results were the most important clinical information needs reported by participants and that may be explained as

prescribers need to ensure that an appropriate antibiotic that covers the causative pathogen is prescribed. Prescribing the appropriate antibiotic quickly that is active against the causative pathogen is very essential and can be life-saving.

In the present study, the most common perceived benefit of CDSS was the ability to suggest an antibiotic regimen. This could be explained by medical staff valuing advice as to prescribing the right antibiotic, in the right dose, for the right duration, at the right frequency and the right regimen. The ability to link to antibiotic guideline was the second most common valued feature of CDSS.

One of the barriers for adopting CDSS is the perception that it limits the prescribers' medical autonomy. Most CDSS utilise practice guidelines which are perceived mainly by senior prescribers as a way to limit their medical autonomy. A study by Cabana and co-workers showed that prescribers feel that guidelines reduce their medical autonomy (Cabana et al., 1999). Halm and co-workers showed that junior prescribers found community acquired pneumonia guidelines more helpful in their work than senior prescribers did (Halm et al., 1999). The majority participants who responded to this questionnaire did not report this perception and showed a positive attitude for the adoption of CDSS. A study by Darr and co-workers found the perceived limitation of medical autonomy as one of the barriers to adopting an EMR-based system (Darr et al., 2003). Another study by Grundmeier and co-workers showed that prescribers hold neutral perceptions regarding the impact of CDSS on their medical autonomy (Grundmeier and Johnson, 1999).

4.7.2 Strengths and limitations

Strengths of this study include that few published reports have attempted to evaluate healthcare professionals' attitudes and perceptions towards CDSS while the majority of previous research has focussed on the effectiveness of CDSS. The CDSS examined in the present study was an antibiotic CDSS that delivered evidence-based guideline algorithms at the point of care in a similar way to the

iApprove system reported by Zaidi and co-workers (Zaidi, 2009). The majority of participants believed that structured prescribing will improve antibiotic prescribing similar to the results from the Zaidi study. A study conducted in Singapore by Chow and co-workers showed that willingness to consult CDSS for common and complex infections (OR=1.68, 95% CI 1.16-2.44) and preference for personal or team decision (OR=0.61, 95% CI 0.43-0.85) were associated with acceptance of CDSS recommendations (Chow et al., 2015). The present study adds to the evidence by exploring prescribers' clinical information needs and perceived preferred features that would maximize adoption. The use of the CDSS system was optional throughout the study period. Therefore, participants were less likely to be affected by hospital policy in their usage of the system.

Limitations of the study include that the response rate was very low 6% despite reminders being sent to increase the response rate. One possible conclusion might be that practitioners were not interested. FY1 prescribers may have not accessed their emails and their rotation may have made them unaware of CDSS. This could explain the low response rate for the questionnaire. It seems that junior prescribers do not care while senior prescribers showed a positive attitude towards CDSS. However, there was representation of participants from different clinical departments across the study site which would help to minimize non-respondent bias. The paucity of reliable and valid tools in the field of medical informatics research has been reported as a major problem encountered by researchers.

4.7.3 Implication for practice and research

While CDSS are becoming more commonly used in implementing guidelines including antibiotic protocols, significant barriers to their adoption exist. The designers of CDSS in future might utilise the perceptions and attitudes of users found in the present study to reflect on the design of CDSS so that it matches their needs and perceptions. The present study measured clinicians' perceptions of an antibiotic CDSS in an NHS Foundation Trust in Birmingham, England. Despite the fact that the study

was conducted at a single Trust, participants came from a range of healthcare professionals. The findings of the present study may be useful for other hospitals in the deployment of CDSS.

4.8 Conclusion

Findings from the present study will be of value to the developers and implementers of the PICS CDSS at the study hospital to help in the implementation and further development of the CDSS in the future. Further studies using similar research tools will improve understanding of the perceptions of medical and non-medical prescribers in their adoption of the CDSS.

Chapter 5: Examining the impact of Structured Prescribing on the volume of antibiotic use in hospitalised patients- retrospective before and after study

5.1 Introduction

Antimicrobial resistance is correlated with inappropriate use of antibiotics. The consumption of antibiotics is an essential driver for the development of AMR (Public Health England, 2014). In this section, the volume of antibiotic use at UHBFT has been examined quantitatively over a period of four years. Continuous measurement with the ability to audit drug use in the hospital provides essential information on antibiotic consumption.

There is no single measure to help understand the prescribing of antibiotics. The only widely accepted unit of measurement that can be utilised across all clinical settings at present is the defined daily doses, which is an internationally recognised measure recommended by the WHO. The defined daily dose is the average maintenance dose of a medicine used for its main indication in adults. The importance of defined daily dose is that it allows for continuous tracking of the volume of antibiotic use over time in studies both nationally and internationally. This chapter examines the importance of CDSS as an influence on the volume of antibiotics used. This chapter includes the results of a pilot implementation of a CDSS at an NHS hospital. At the hospital, pharmacists provide monthly audit results of the quantities of antibiotic dispensed. Antibiotic quantities dispensed are collected by an Ascribe database. This database is embedded within PICS system and internally audit monthly use of antibiotics. In order to improve the focus on antibiotics, the present study was conducted to examine the influence of CDSS on antibiotic use at UHBFT.

5.2 Aims and objectives

The aim of the present study was to examine the impact of CDSS on the volume of antibiotic use at UHBFT before and after CDSS implementation in hospitalised patients.

5.3 Objectives

- Conduct a cross sectional before and after study to examine the impact of CDSS on all antibiotic classes
- Calculate the defined daily dose corrected per 1000 bed-days for each class of antibiotics
- Conduct regression analysis for each class of antibiotics to examine the patterns of antibiotic use before and after the implementation of CDSS
- Conduct descriptive statistical analysis for each class of antibiotics

5.4 Methods

In the present study, the CDSS provided evidence-based, algorithm-directed guidelines to facilitate the prescribing of antibiotics. It was hypothesized that structured prescribing (SP) would significantly influence the pattern of antibiotic use. Antibiotic recommendations were based on the hospital's guideline resources. The analysis was conducted on hospitalised patients who occupied beds

5.4.1 Setting and intervention

University Hospital Birmingham NHS Foundation Trust (UHBFT) is a tertiary care hospital with 1200 beds. The electronic prescribing system used at the hospital is called 'patient information communication system' (PICS). The system has decision support functionality ranging from alerts of inappropriate dosing, dashboard presentation of relevant data and access to clinical guidelines. Structured prescribing was a CDSS embedded within PICS and provided decision support for prescribing antibiotics. The system was developed by a group of infectious disease physicians, microbiologists, infection control specialists, pharmacists and informatics experts. It utilized patient information such as weight, renal function, allergies and microbiology susceptibility results to recommend an evidence-based, algorithm directed antibiotic recommendation to a prescriber. A comprehensive antibiotic database provided recommendation for appropriate dose and dosing intervals for selected antibiotics as well as dose modification according to renal and hepatic function.

Use education about the system was conducted by a group of pharmacists, the PICS team and informatics team who played an essential role through frequent informal teaching seminars directed at senior and junior prescribers. Structured prescribing was implemented in June 2008 and was taken out of use in June 2014 owing to issues related to workflow and screen layout. This potentially could impact on the results obtained from the before and after study. One of the limitations of the before and after study is that it is not possible to be certain that the results were attributable to changes in the system rather than external influences. There may have been other factors that affected the way structured prescribing worked. There may have been changes in morbidity over time which might have impacted on trends in antibiotic use. There may have been variation in the incidence of complex infections that required the use of more broad-spectrum antibiotics. Prescribers may have overlooked structured prescribing recommendations and prescribed more broad-spectrum antibiotics. There may have been policy for prescribing certain antibiotics when structured prescribing was live. Structured prescribing was not promoted so the results reflect almost unsolicited uptake. Other potential factors that could have influenced antibiotic use such as changes in formulary drugs and changes in treatment guidelines which may or may not have happened.

5.4.2 Study design and data collection

An observational, retrospective before and after study was used to assess the impact of structured prescribing on the volume of antibiotic consumption. The 2-year period with the structured prescribing intervention began in June 2012 and ended in May 2014 while the period without-intervention commenced in June 2014 and ended in June 2016. The outcome measure used was the rate of overall antibiotic consumption measured as the defined daily dose (DDD) per 1000 occupied bed-days. No ethical approval was required for this work package.

Information on the use antibiotics prescribed in UHBFT was obtained from the ASCRIBE database embedded in PICS. Hospital pharmacies in UHBFT provide aggregate monthly data for all medicines issued to patients via ASCRIBE PICS. No data was included for patients not occupying a bed and the data provided was only for in-patients. All day case areas and A&E were excluded. The analysis was conducted on hospitalised patients occupying a bed. A good number of the drugs would not be used in clinics i.e. patients not in a bed. The bed-days denominator is valid given the low number of patients not occupied in bed. The data only included in-patients then the use of bed-days as a denominator is valid

Antibiotics were grouped according to the BNF classification. Data on antibiotic consumption were converted to WHO DDDs. The classification of data on antibiotic consumption was based on the Anatomical Chemical (ATC) classification system. This is the international classification system aimed at identifying the therapeutic ingredient of all medicines available for human use. The denominator used for calculating the rate of consumption was occupied bed-days normalised to 1000 bed days. The data of the denominator was also extracted from the ASCRIBE database embedded within PICS. Data on any microorganisms' outbreaks that could have happened during the periods with and without structured prescribing was obtained from the microbiology department and the antimicrobial pharmacist. No ethical approval was required for this work package.

5.4.3 Statistical analysis

A linear regression was applied with the dependent variable being antibiotic consumption in DDD/1000 bed-days and the explanatory variable being month of the year. Student t- test was applied with the dependent variable being antibiotic consumption DDD/1000 bed-days and the explanatory variable being month of the year. Student's t-test was chosen to compare between two groups and to measure the mean difference between the two groups (with and without structured prescribing).

Statistical significance was accepted for results where $p < 0.05$. Pearson's correlation was applied to test the correlation between variables by measuring R^2 values for the periods with and without structured prescribing.

There are many statistical methods for testing the normality of a distribution such as visual methods. However, visual methods are often unreliable. Histogram plots are usually used to check normality of a distribution. Other tests to check the normality of a distribution can be conducted using SPSS such as Shapiro-Wilk test. This test “compares the scores in the sample to a normally distributed set of scores with the same mean and standard deviation; the null hypothesis is that sample distribution is normal. If the test is significant, the distribution is non-normal” (Ghasemi and Zahediasl, 2012). In the present the study, the Shapiro-Wilk test was conducted to check the normality of distribution. The level of significance of mean difference is displayed as the number of asterisks as follows:

- one asterisk (*) represents significant level where $p \leq 0.05$
- two asterisks (**) represent very significant level where $p \leq 0.01$
- Three asterisks (***) represent highly significant level where $p \leq 0.001$
- NS represents not significant level where $p > 0.05$

5.5 Results

The four-year trend in total antibiotic use in UHBFT between 2012 and 2016 is shown in Figure 16. Sixty-six different antibiotics were prescribed: the classes with the highest incidence of use were penicillins and macrolides. From June 2012 to June 2016, combined antibiotic usage increased by 13.1% from 1436.3 to 1624.85 DDD/1000 bed-days. From June 2012 to June 2016, the predominant antibiotic class used in UHBFT was penicillins shown in Figure 17. The trends for the total consumption of all antibiotics are shown in Figure 17 and demonstrate an incremental increase in use

for all antibiotics classes except for tetracyclines, quinolones and antimycobacterials whereas aminoglycosides usage remained stable.

Overall from June 2012 to June 2014, there was a trend of increased antibiotic prescribing which was more pronounced during the period of structured prescribing as shown in Figure 18. The slope of antibiotic consumption during the period with structured prescribing was steeper than the slope during the period without structured prescribing. There was a positive linear relationship between time and DDD/1000 bed days with weak correlations for the periods with structured prescribing ($R^2=0.2843$) and without structured prescribing ($R^2=0.1112$).

5.5.1 Normality of the distribution

Graphical methods can be used to check the normality of a distribution. Plotting a histogram indicates of the shape of the distribution. A normal approximation curve can be added to the graph. There are also other tests for testing the normality of a distribution namely Shapiro Wilk W test. This test assumes that the data is normally distributed which is the null hypothesis. If the p value is not significant then the null hypothesis is maintained and the distribution is then normal. If the p value is significant ≤ 0.05 , then the null hypothesis is rejected and the distribution is not normal. In the present study, the p values were 0.157 and 0.084 which were not significant, so the null hypothesis remained and the distribution of the data was considered normal (See Figures 14 and 15).

Figure 14: Distribution of data for all antibiotics for the period with structured prescribing

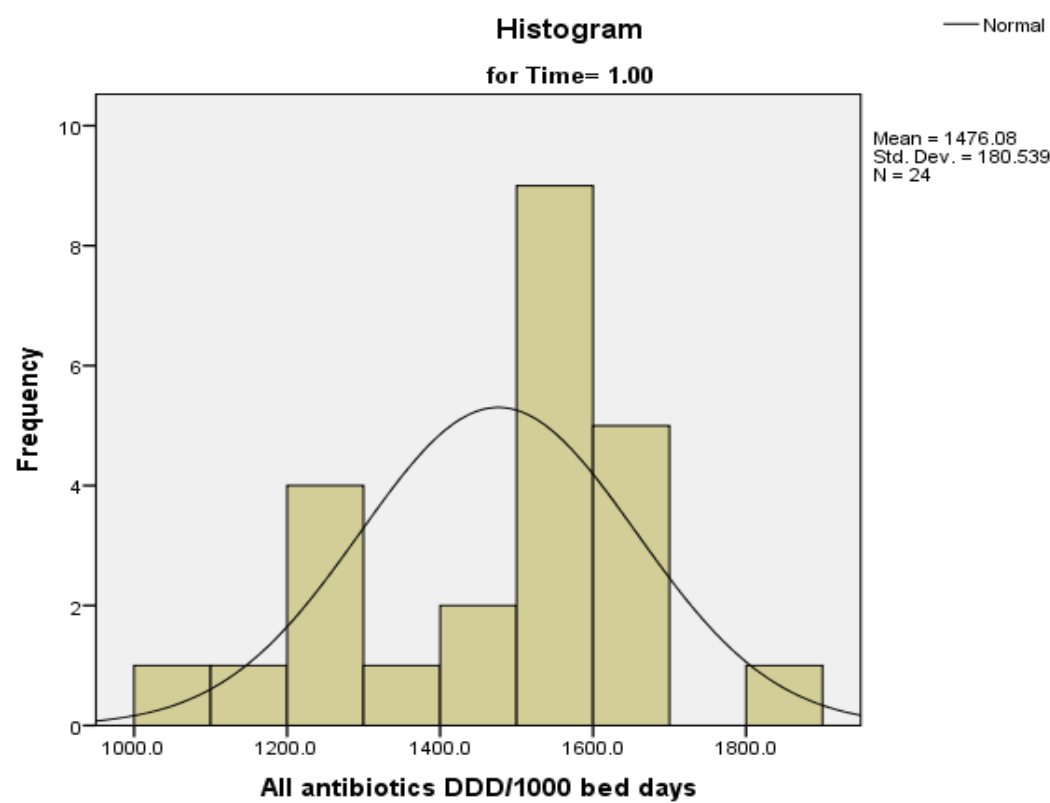
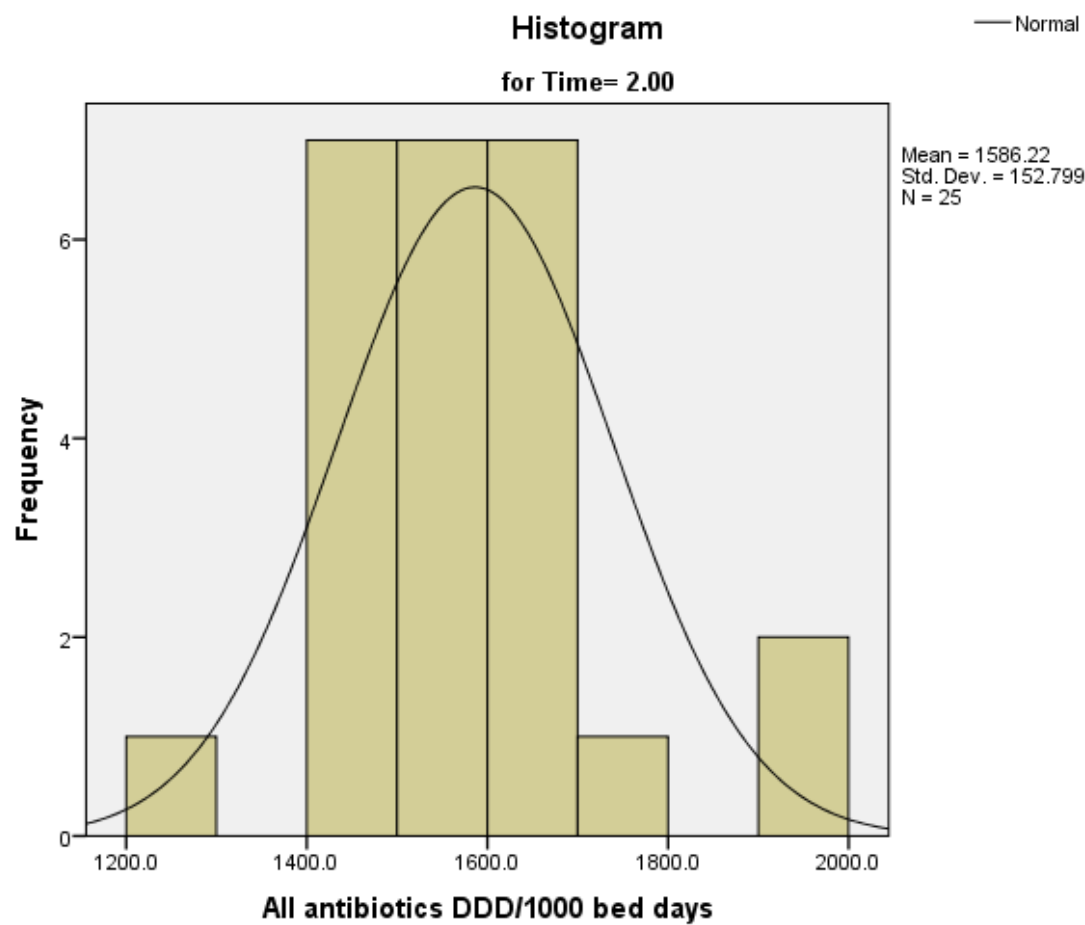
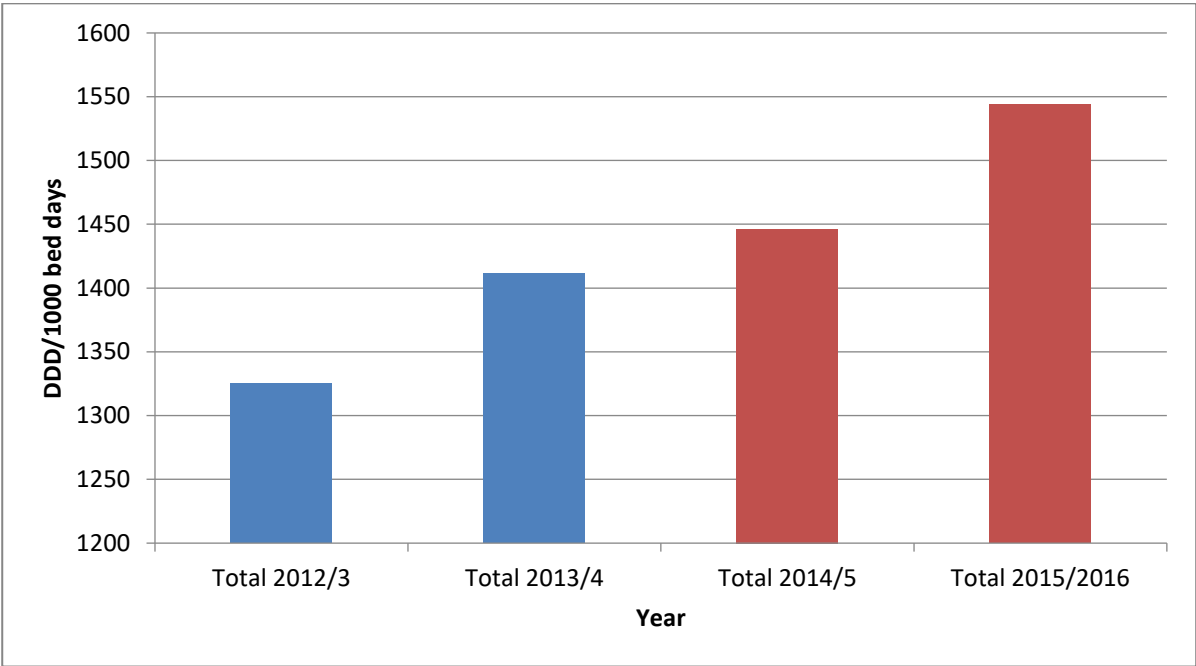


Figure 15: Distribution for data of all antibiotics for the period without structured prescribing



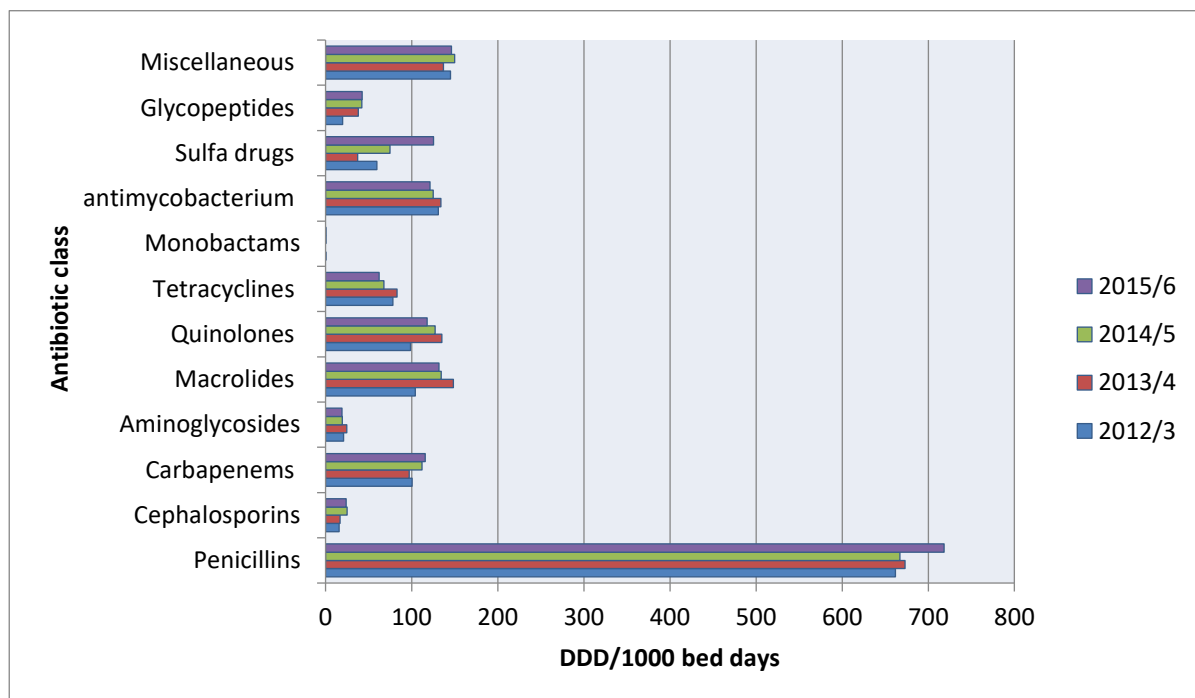
The four-year trend in total antibiotic use at UHBFT between 2012 and 2016 is shown in Figure 16. From June 2012 to June 2016, combined antibiotic usage increased by 13.1% from 1436.3 to 1624.85 DDD/1000 bed-days.

Figure 16: Consumption of total antibiotics, expressed as DDD per 1000 bed days, 2012-2016



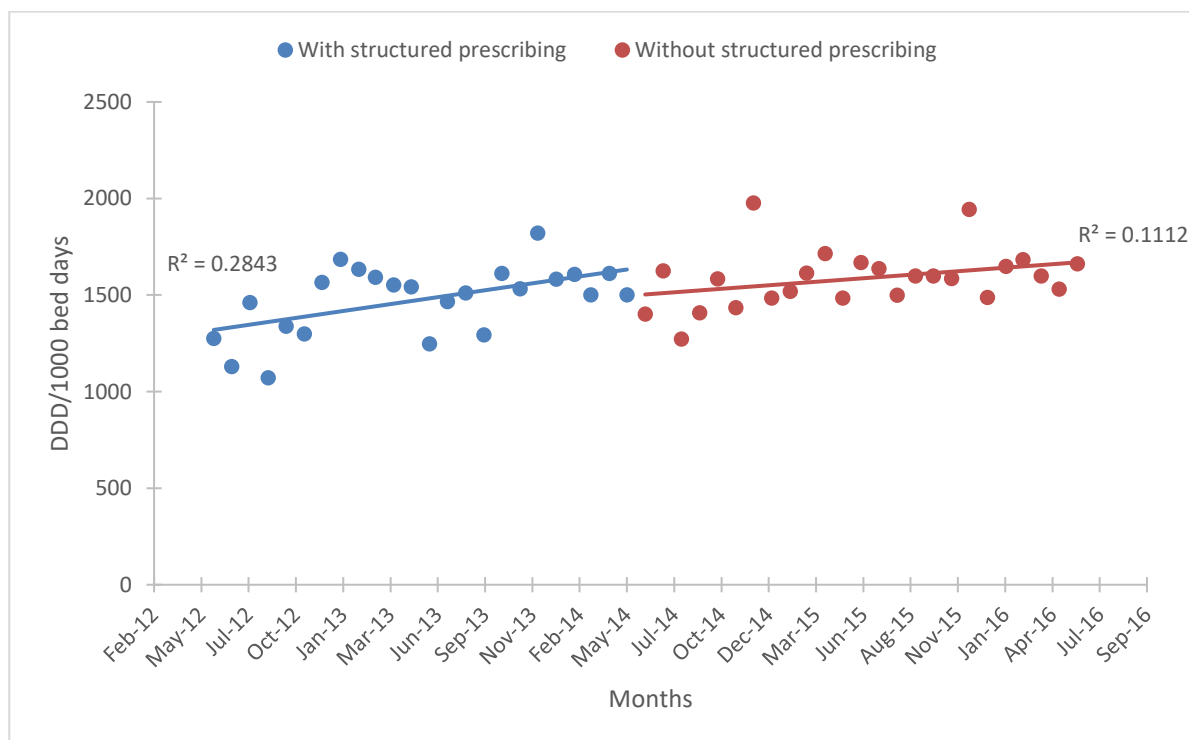
Sixty-six different antibiotics were prescribed: the classes with the highest incidence of use were penicillins and macrolides. From June 2012 to June 2016, the predominant antibiotic used at UHBFT were penicillins shown in Figure17. The trends for the total consumption of all antibiotics demonstrate an increase in usage for all antibiotics classes except for tetracyclines, quinolones and antimycobacterials whereas aminoglycosides usage remained stable.

Figure 17: Total antibiotic consumption by group, expressed as DDD per 1000 bed days, 2012-2016



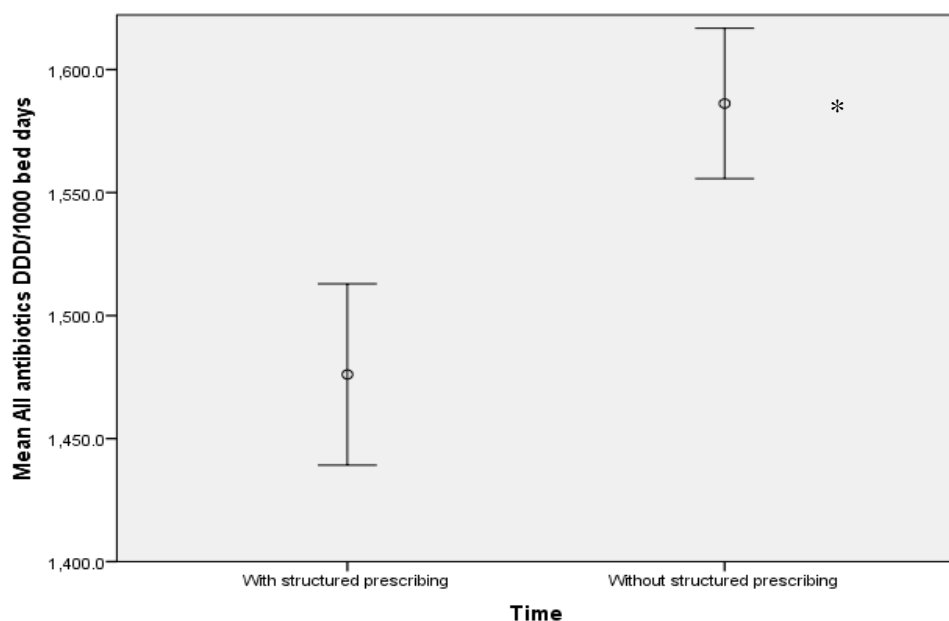
Overall from June 2012 to June 2014, there was a trend of increased antibiotic prescribing which was more pronounced during the period with structured prescribing as shown in Figure 18. In figure 18, there appears to be an increase in the use of all antibiotics between the periods with and without structured prescribing. This increase was more pronounced during the period with structured prescribing. There was a weak positive correlation between DDD/1000 bed days and time in the periods with structured prescribing ($R^2 = 0.2843$) and without structured prescribing ($R^2 = 0.1112$).

Figure 18: Monthly consumption of all antibiotics reported as DDD/1000 bed days. Trend lines established by linear regression before and after deployment of structured prescribing are shown



Data in figure 19 shows that there was a difference of means of (-110.14 DDD/1000 bed days) of the total usage of antibiotics in the period with and without structured prescribing and this was statistically significant ($p=0.026$).

Figure 19: Mean difference for all antibiotic use for the periods with and without structured prescribing



Comparisons of the means of DDD/1000 bed days of all antibiotics and standard error bars for the periods with and without structured prescribing

*indicates significant $p \leq 0.05$

The impact of structured prescribing on the amount of antibiotic prescribed was divided into three categories:

- 1- Antibiotics where structured prescribing is associated with a decrease in their use (Structured prescribing reduced their use).
- 2- Antibiotics where structured prescribing is associated with an increase in their use (Structured prescribing increased their use)
- 3- Antibiotics where structured prescribing is associated with no change in their use (Structured prescribing had no/ neutral impact on their use).

No outbreaks of microorganisms occurred during the periods with and without structured prescribing.

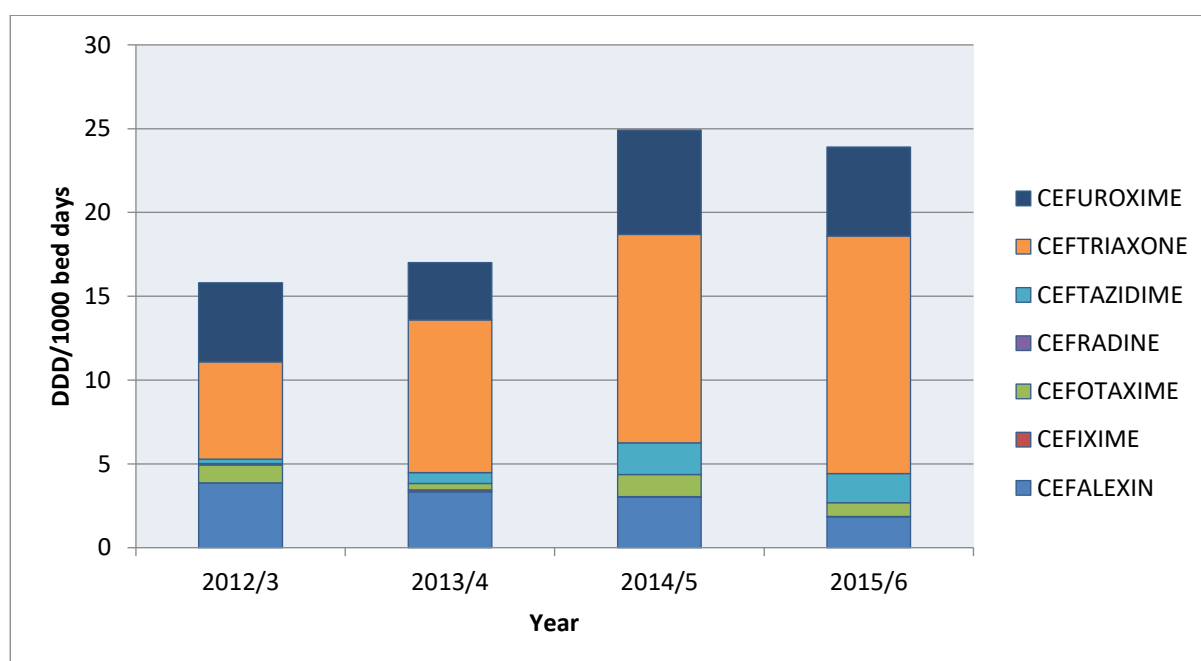
5.5.2 Antibiotics where structured prescribing is associated with a decrease in their use

5.5.2.1 Cephalosporins

Cephalosporins are a class of antibiotics that were developed in the 1960s. They are mainly active against Gram-positive microorganisms such as staphylococci and streptococci. The indications for which cephalosporins are used are urinary tract infection, community acquired pneumonia and intraabdominal infections. However, their use has decreased due to the risk of developing clostridium infections in patients receiving them (Public Health England, 2014).

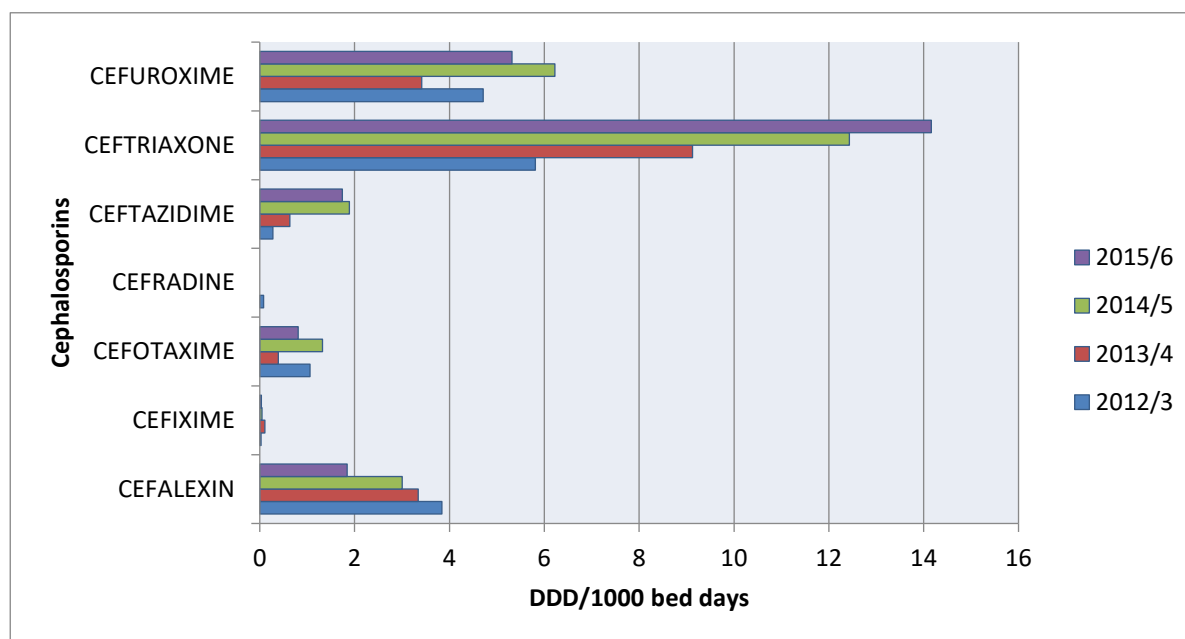
From June 2012 to June 2016, the volume of cephalosporins prescribed increased by 50% from 15.9 to 23.9 DDD/1000 bed days; this occurred mainly between June 2013/2014 to June 2014/2015 (an increase of 41.1%).

Figure 20: Consumption of cephalosporins, expressed as DDD per 1000 bed days, 2012-2016



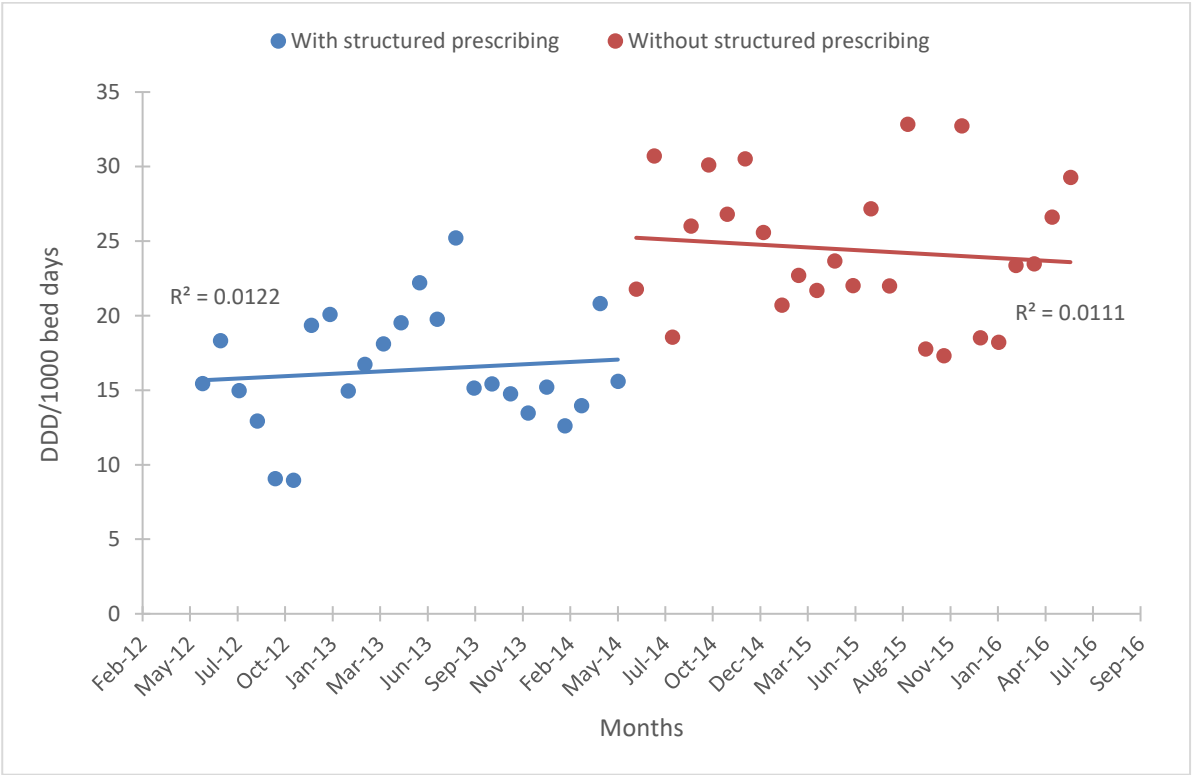
The top seven most commonly used antibiotics in this class are presented in Figure 21. Ceftriaxone (37%) was the most commonly prescribed cephalosporin followed by cefuroxime (30%). The use of ceftriaxone increased over the four years from 5.8 to 14.2 DDD/1000 bed days (an increase of 144.8 %). The use of injectable cephalosporins increased compared to oral cephalosporins

Figure 21: Cephalosporins consumption by group, expressed as DDD per 1000 bed days, 2012-2016



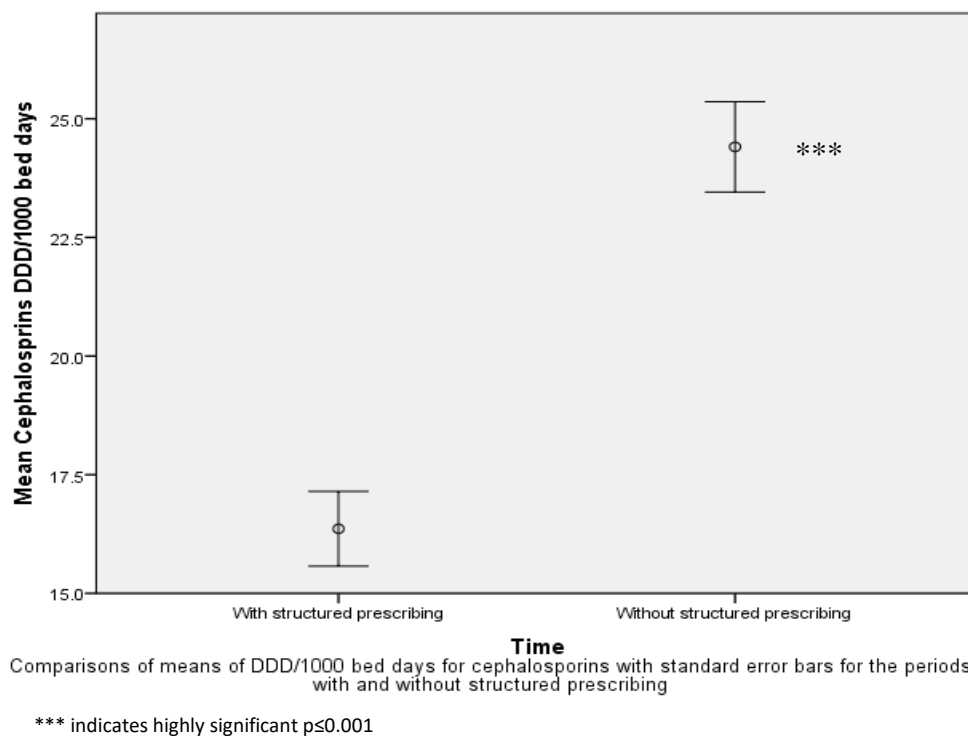
In figure 22, there is an increase in the use of cephalosporins between the periods with and without structured prescribing. This increase was more pronounced in the period without structured prescribing. However, there is no correlation between cephalosporin consumption and time for the periods with structured prescribing ($R^2=0.0122$) and without structured prescribing ($R^2=0.0111$).

Figure 22: Monthly consumption of cephalosporins reported as DDD/1000 bed days. Trend lines established by linear regression before and after deployment of structured prescribing are shown



The mean difference and standard error bars in Figure 23 of all antibiotics shows a mean difference of -8.04 DDD/1000 bed days in the period with and without structured prescribing and this was statistically significant ($p < 0.001$).

Figure 23: Mean difference for cephalosporins use for the periods with and without structured prescribing

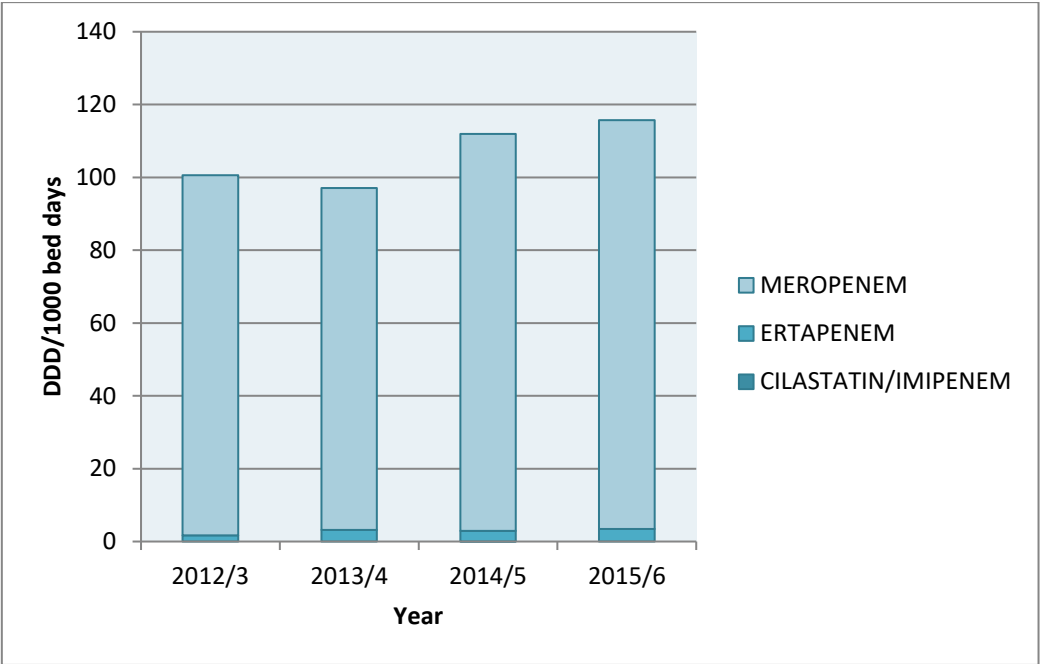


5.5.2.2 Carbapenems

Carbapenems are a class of antibiotics that are categorised as the last resort in treatment of serious Gram-negative infections (Public Health England, 2014). These antibiotics have a broad-spectrum activity and are resistant to beta-lactamase enzymes because of their structure. However, resistance to this class has developed recently by the production of carbapenemases which disable the structure of these antibiotics. Carbapenems are effective against infections caused by Gram-negative bacteria such as those found in patients in intensive care unit, transplant and cancer units (Public Health England, 2014).

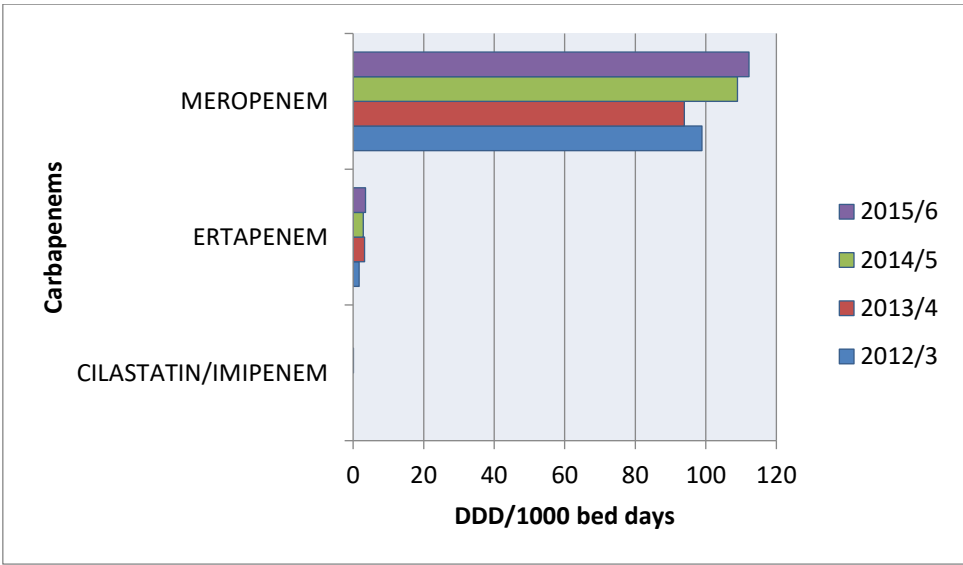
The use of carbapenems increase by 15.3% between June 2012 and June 2016 from 100.6 to 115.7 DDD/1000 bed days; this mostly occurred between June 2013/4 to June 2014/5 (an increase of 15.3%) (see Figure 24).

Figure 24: Consumption of carbapenems expressed as DDD per 1000 bed days, 2012-2016



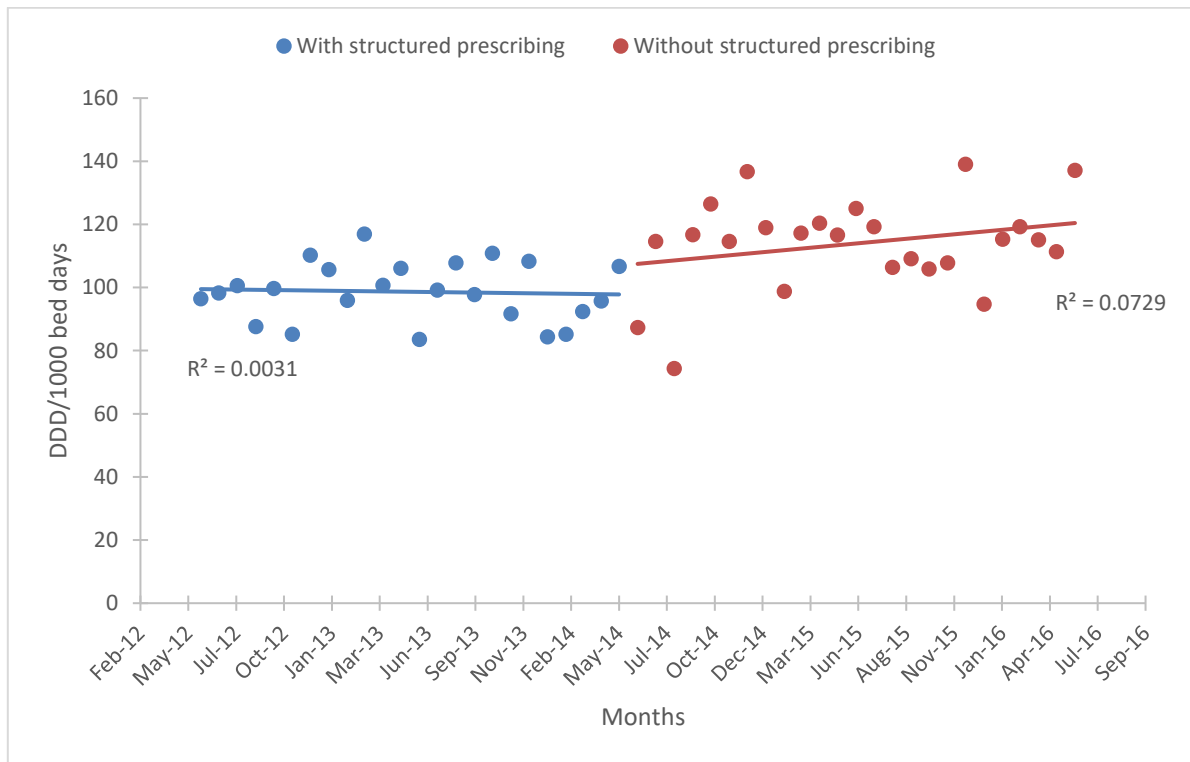
Meropenem was the most commonly used carbapenem over the four years accounting for almost 100% of use. Use of meropenem increased by 13.5% from 98.9 to 112.2 DDD/1000 bed days. Ertapenem and imipenem were used less frequently (See Figure 25).

Figure 25: Carbapenems consumption by group, expressed as DDD per 1000 bed days, 2012-2016



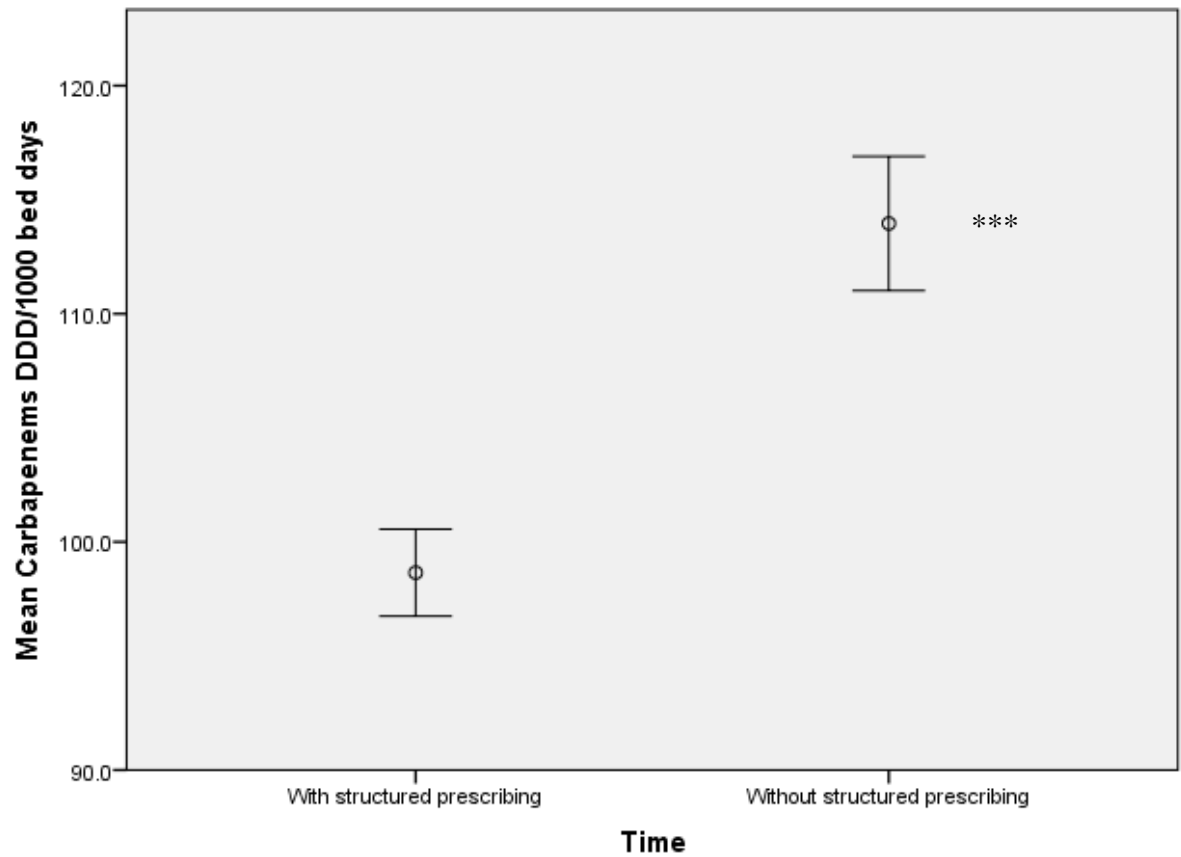
In figure 26, there was an increase in the use of carbapenems between the periods with and without structured prescribing. This increase was more pronounced in the period without structured prescribing. Given the low R^2 values there is no correlation between the variables for the period with structured prescribing ($R^2 = 0.0031$) and without structured prescribing ($R^2 = 0.0729$).

Figure 26: Monthly consumption of carbapenems reported as DDD/1000 bed days. Trend lines established by linear regression before and after deployment of structured prescribing are shown



The mean difference and standard error bars in figure 27 show that there was a mean difference of 15.3 DDD/1000 bed days in the periods with and without structured prescribing and this was statistically significant ($p < 0.001$).

Figure 27: Mean difference for carbapenems use for the periods with and without structured prescribing



Comparisons of means of DDD/1000 bed days for carbapenems and standard error bars for the periods with and without structured prescribing
*** indicates highly significant $p \leq 0.001$

5.5.2.3 Sulfonamides

This class of antibiotics can be administered either individually or in combination. They have a wide range of spectrum covering bacteria, fungi and protozoa. They exert their action by inhibiting the synthesis of folic acid in pathogens.

The consumption of sulfonamides increased between June 2012 and June 2016 by 75% from 23 to 92 DDD per 1000 bed days, the increase mainly occurred between June 2013/4 to June 2014/5. Sulfasalazine is used mainly as anti-rheumatic and has some antibiotic activity.

Figure 28: Consumption of sulfonamides expressed as DDD per 1000 bed days, 2012-2016

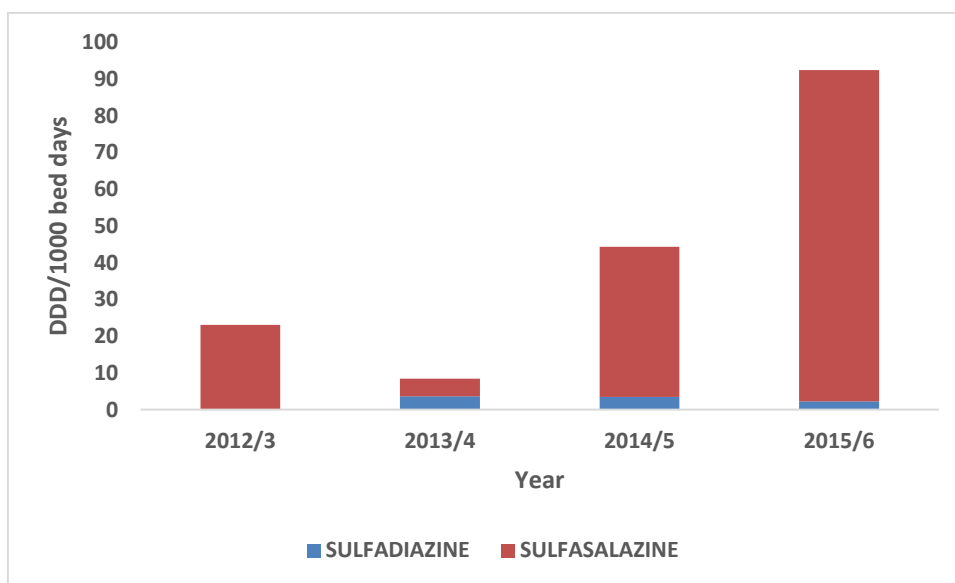
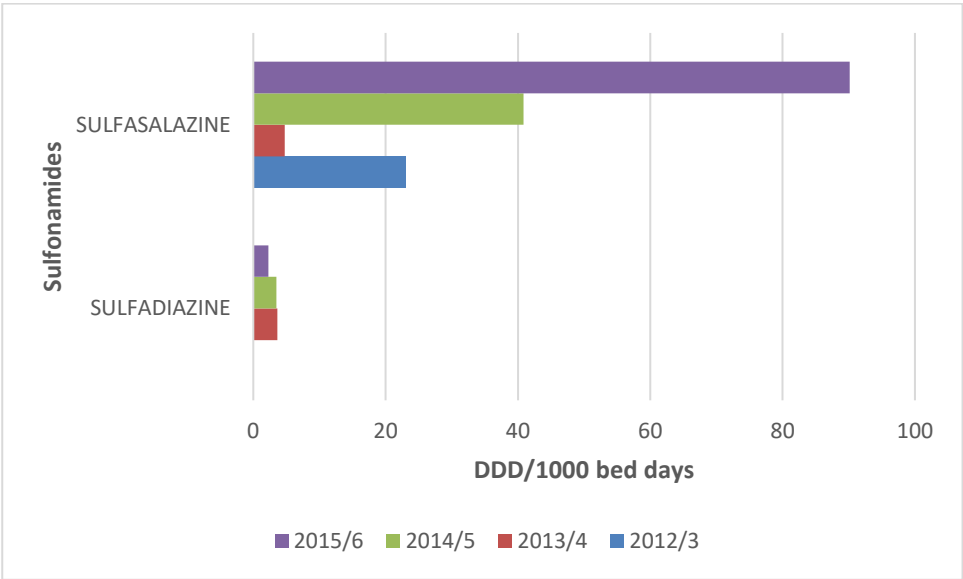
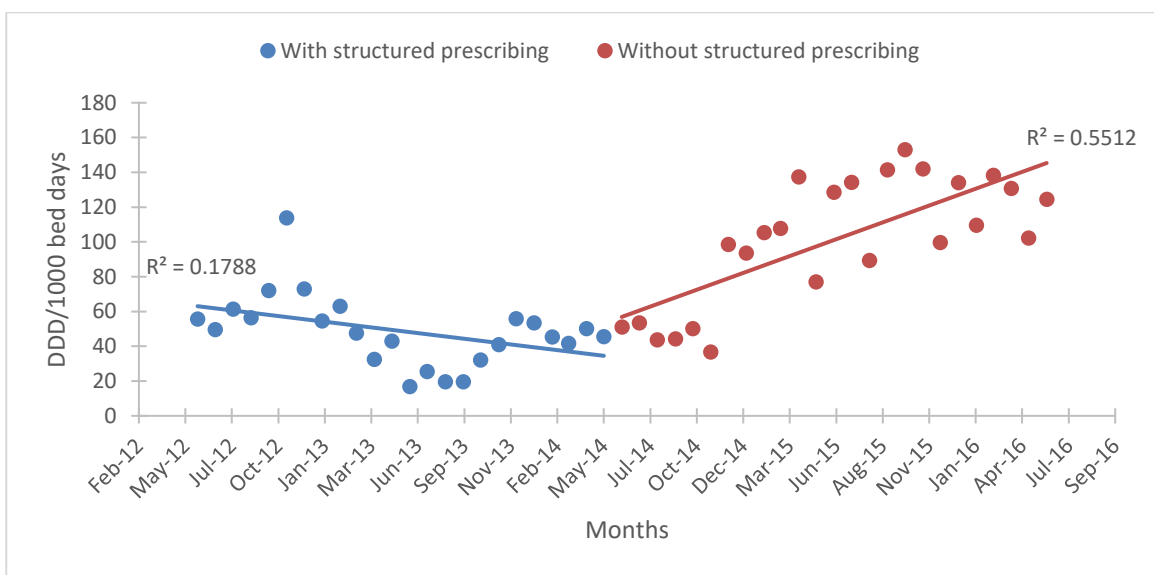


Figure 29: Sulfonamides consumption by group, expressed as DDD per 1000 bed days, 2012-2016



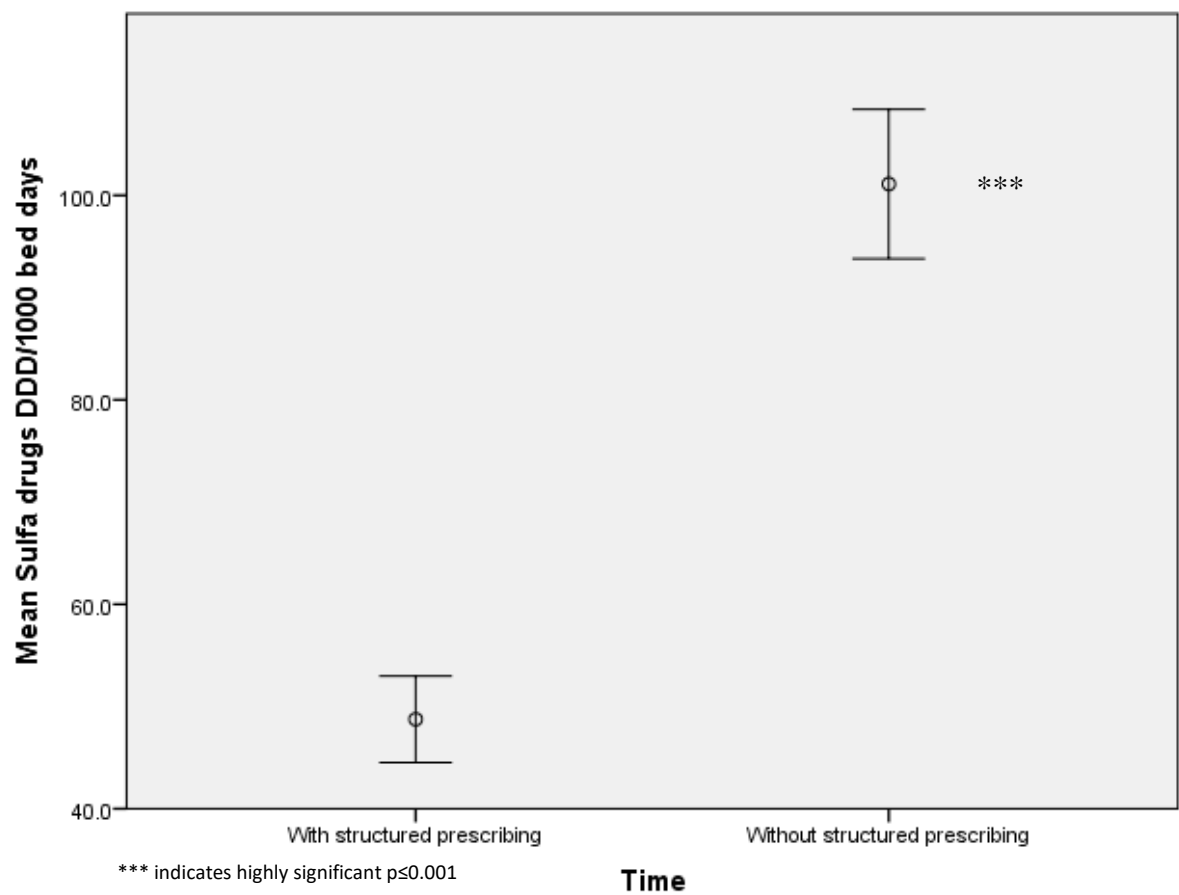
In figure 30, there was an increase in the use of sulfonamides in both the periods with and without structured prescribing. The increase was more pronounced in the period without structured prescribing. There was a negative correlation between the variables for the period with structured prescribing ($R^2= 0.1778$) and a positive correlation for the period without structured prescribing ($R^2=0.5512$).

Figure 30: Monthly consumption of sulfonamides reported as DDD/1000 bed days. Trend lines established by linear regression before and after deployment of structured prescribing are shown



The mean difference and standard error bars shown in figure 31 show that there was a mean difference of -52.35 DDD/1000 bed days in the periods with and without structured prescribing and this was statistically significant ($p < 0.001$).

Figure 31: Mean difference for sulfonamides use for the periods with and without structured prescribing

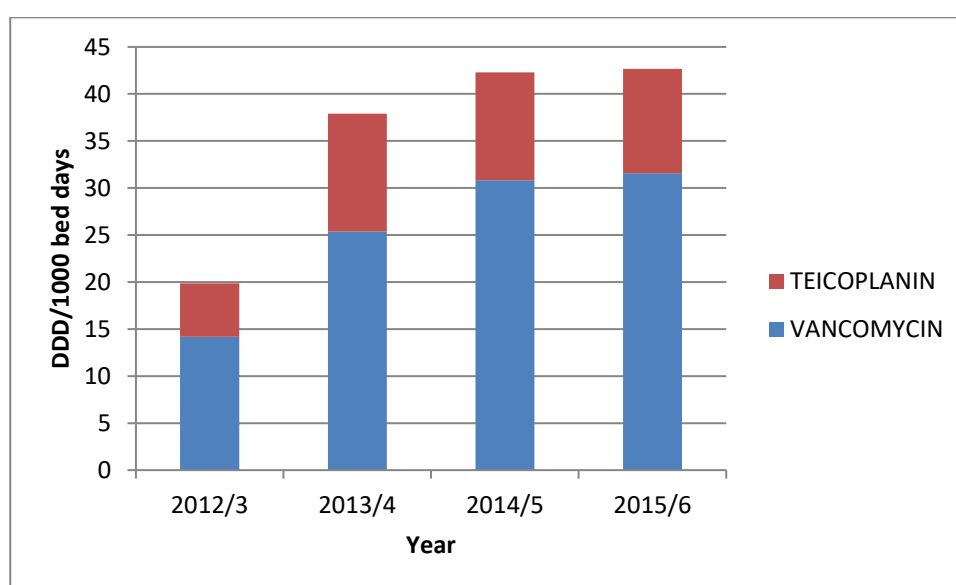


5.5.2.4 Glycopeptides

This class of antibiotic is used to treat infections due to resistant Gram-positive bacteria, such as MRSA, enterococci or coagulase negative staphylococcus (Public Health England, 2014).

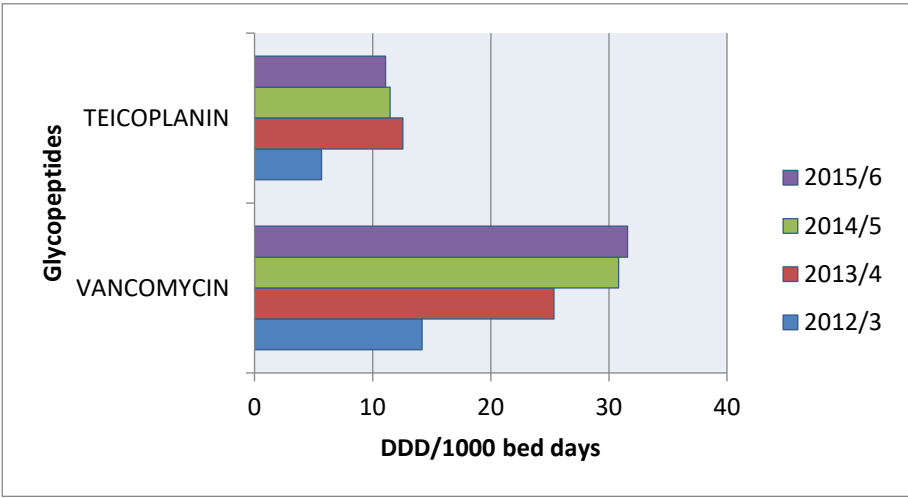
Between June 2012 and June 2016, there was an increase in the use of glycopeptides of (114.6%) from 19.9 to 42.7 DDD/1000 bed days.

Figure 32: Consumption of glycopeptides, expressed as DDD per 1000 bed days, 2012-2016



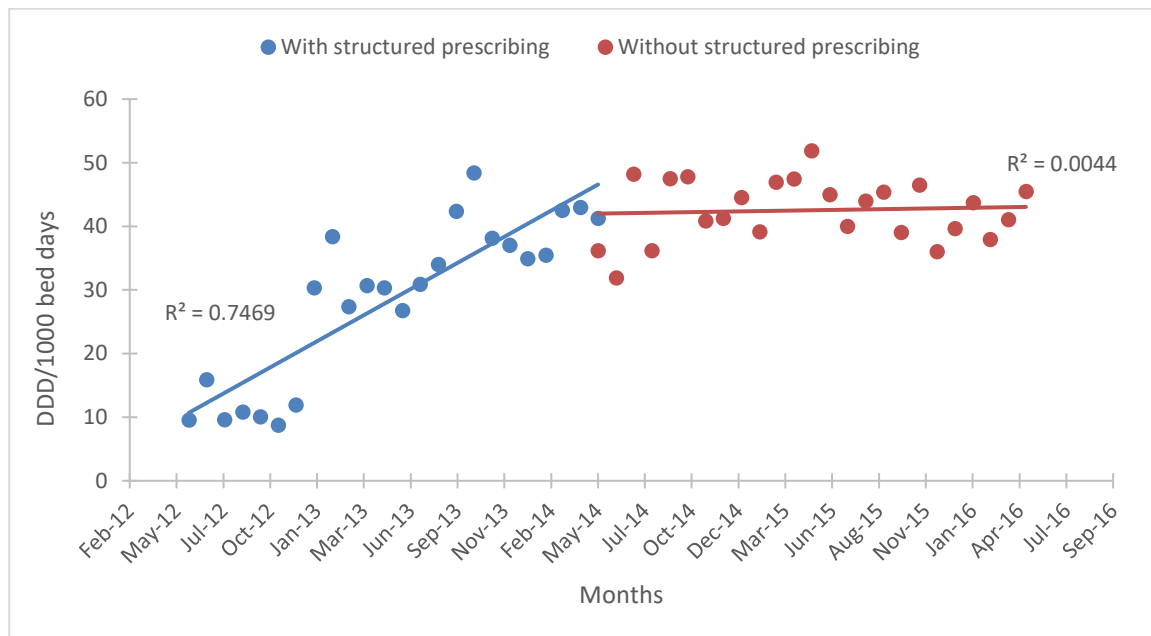
Vancomycin was the most commonly used glycopeptide and accounted for 71% followed by teicoplanin and accounted for 29%. The use of vancomycin increased over the four years from 14.2 to 31.6 DDD per 1000 bed days (an increase of 122.5%). See figure 33a. The use of oral vancomycin increased over the four years period shown in figure 33b

Figure 33: Glycopeptides consumption by group, expressed as DDD per 1000 bed days, 2012-2016



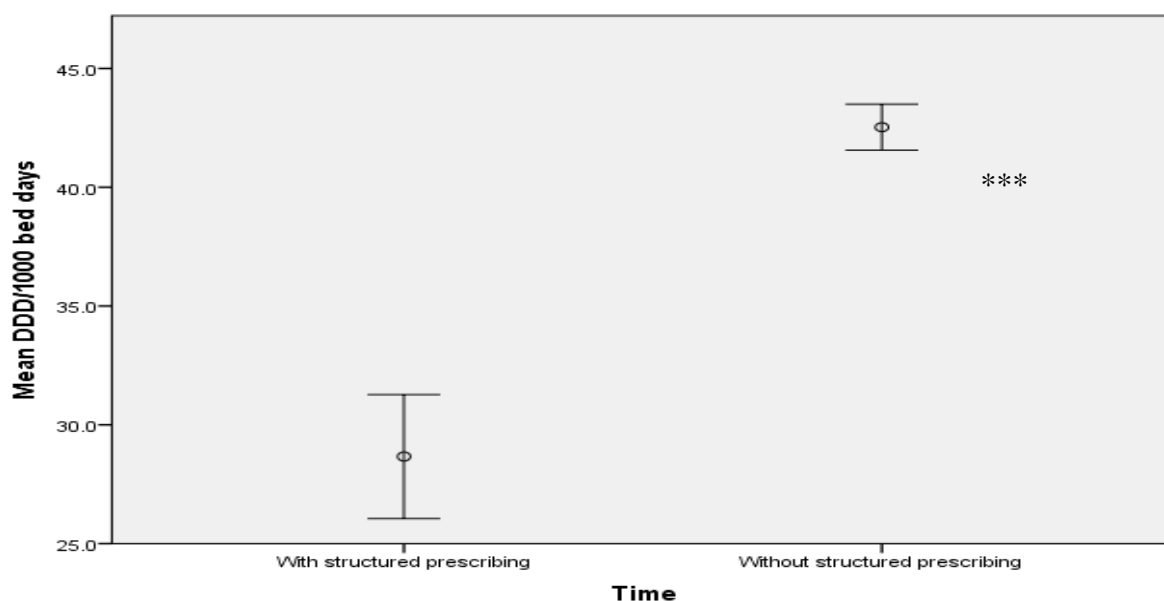
In figure 34, there was an increase in the use of glycopeptides during both the periods with and without structured prescribing. This increase was more pronounced in the period without structured prescribing. There was a positive correlation between the variables for the period with structured prescribing ($R^2 = 0.746$) and a weak correlation for the period without structured prescribing ($R^2 = 0.0044$).

Figure 34: Monthly consumption of glycopeptides reported as DDD/1000 bed days. Trend lines established by linear regression before and after deployment of structured prescribing are shown



The mean difference and standard error bars shown in figure 35 show that for glycopeptides that there was a mean difference of -13.86 DDD/1000 bed days between the periods with and without structured prescribing and this was statistically significant ($p < 0.001$).

Figure 35: Mean difference for glycopeptides use for the periods with and without structured prescribing



Comparison of the means of DDD/1000 bed days for glycopeptides and standard error bars for the periods with and without structured prescribing

5.5.3 Antibiotics where structured prescribing is associated with an increase in their use

5.5.3.1 Aminoglycosides

This class of antibiotics are used for treating Gram-negative infections and used as part of the regimen for treating both sepsis and urinary tract infections. They are also used in combination with penicillins and glycopeptides for treating infections caused by staphylococcus and enterococci such as endocarditis (Public Health England, 2014). They can also be used as an inhaled dosage form for treating infections such cystic fibrosis (Public Health England, 2014).

The consumption of aminoglycosides decreased from 21 to 19.1 DDD/1000 bed days (a decrease of 9%). The top five aminoglycosides used are presented in Figure 36. Gentamicin was the most

commonly used aminoglycoside agent and accounted for 80% of all aminoglycosides used. The use of gentamicin decreased over the four-year period from 17.3 to 15.2 DDD per 1000 bed days (a decrease of 12%). Streptomycin is also used as an antimycobacterial.

Figure 36: Consumption of aminoglycosides, expressed as DDD per 1000 bed days, 2012-2016

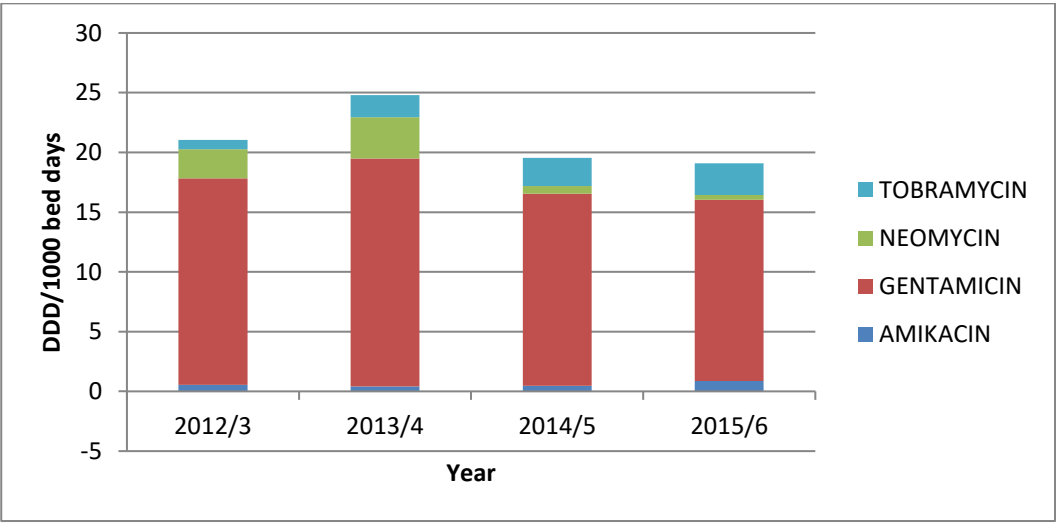
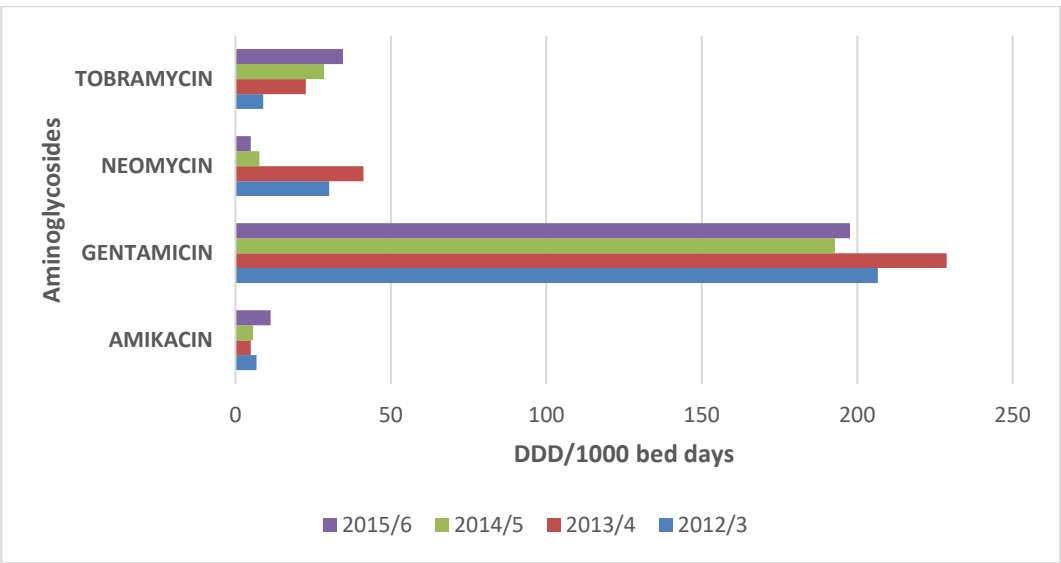
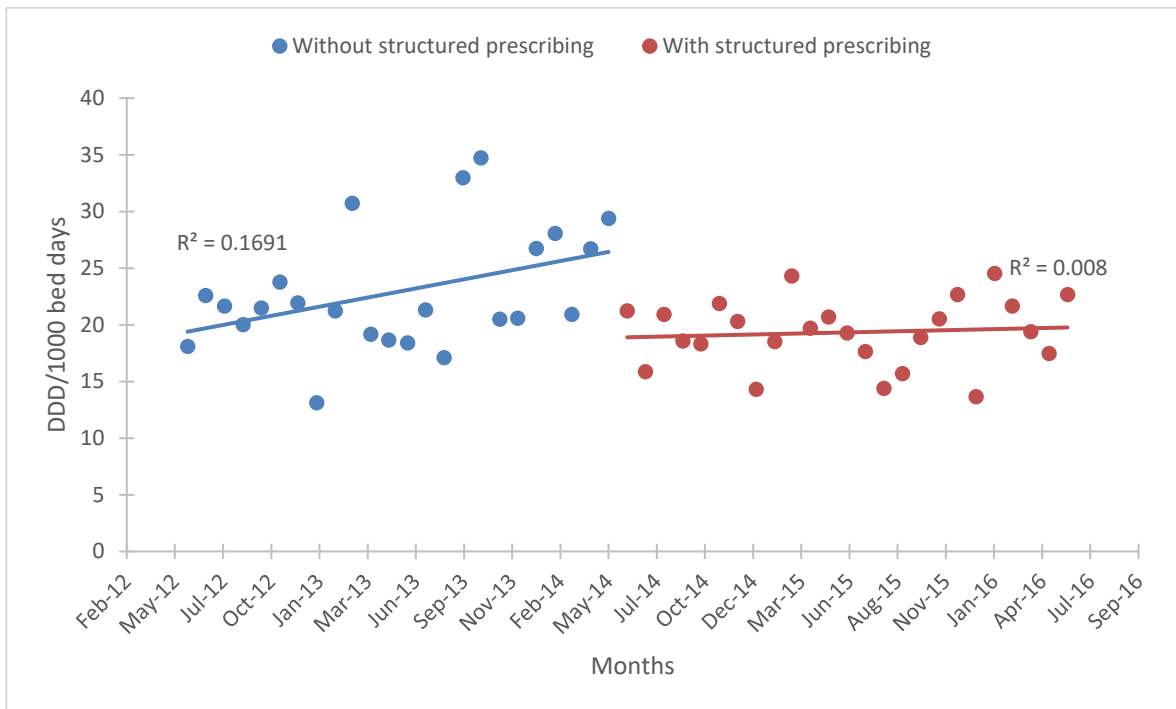


Figure 37: Aminoglycosides consumption by group, expressed as DDD per 1000 bed days, 2012-2016



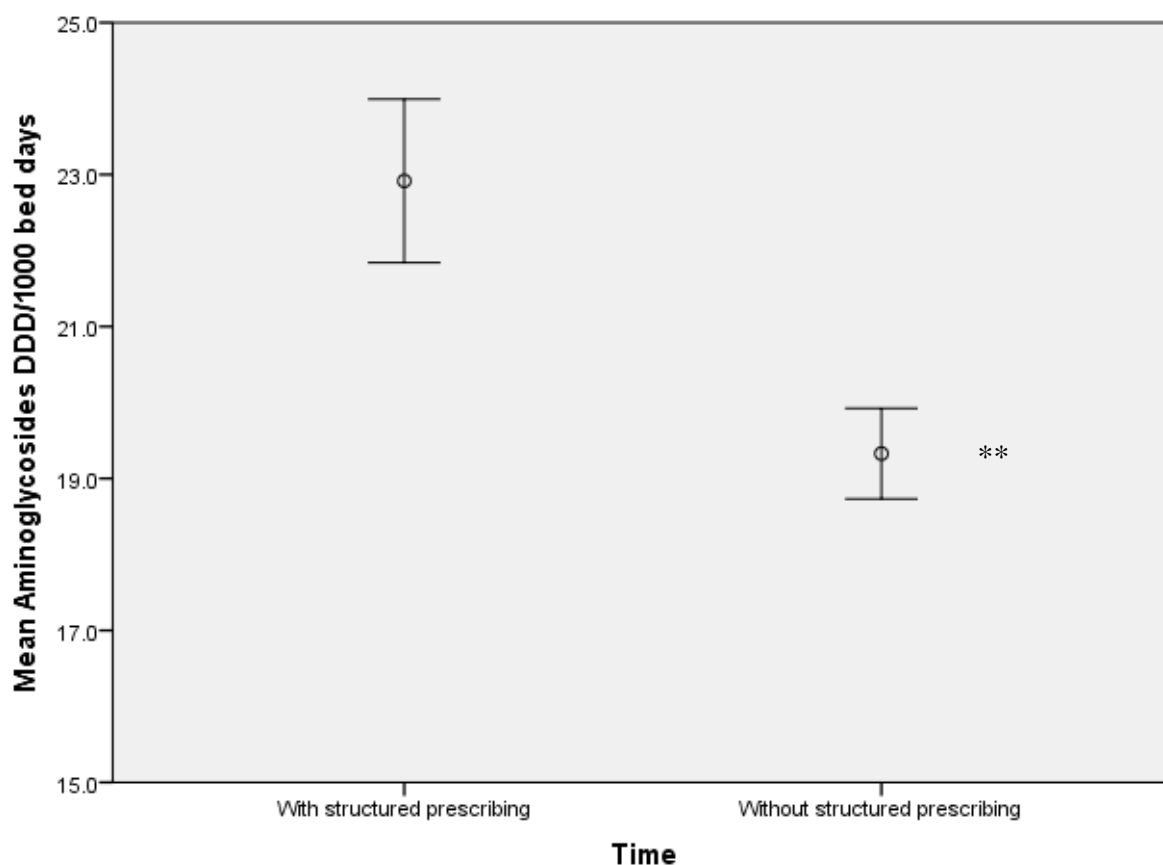
In figure 38, there is an increase in the use of aminoglycosides in the periods with structured prescribing and a decrease in use in the period without structured prescribing. There was a weak positive correlation between the variables for the period with structured prescribing ($R^2= 0.169$) and a weak negative correlation for the period without structured prescribing ($R^2=0.0008$).

Figure 38: Monthly consumption of aminoglycosides reported as DDD/1000 bed days. Trend lines established by linear regression before and after deployment of structured prescribing are shown



The mean difference and standard error bars shown in figure 39 for aminoglycosides show that there is a mean difference of 3.58 DDD/1000 bed days which is statistically significant ($p=0.005$).

Figure 39: Mean difference for Aminoglycosides use for the periods with and without structured prescribing



Comparisons of mean of DDD/1000 bed days for aminoglycosides and standard error bars for the periods with and without structured prescribing

** indicates very significant $p \leq 0.01$

5.5.3.2 Tetracyclines

Tetracyclines are class of antibiotics used to treat Gram-positive infections. They are used for treating acne, sinusitis, bronchitis, exacerbation of chronic obstructive pulmonary disease and pneumonia (Public Health England, 2014).

The use of tetracyclines decreased from 78.3 to 61.1 DDD per 1000 bed days between June 2012 to June 2016. In 2013/4, the use of tetracyclines increased slightly by 5.9% over the previous year.

Doxycycline was the most commonly used tetracycline and accounted for 97% of all tetracyclines prescribed. The use of doxycycline decreased from 77.2 to 58.2 DDD per 1000 bed days (a decrease of 24.6%) over the four-year period. Demeclocycline is used for the treatment of syndrome of inappropriate antidiuretic hormone (SIADH) as it is rarely prescribed as an antibiotic, but it has antibiotic activity and wide use may lead to resistance to other tetracyclines.

Figure 40: Consumption of tetracyclines, expressed as DDD per 1000 bed days, 2012-2016

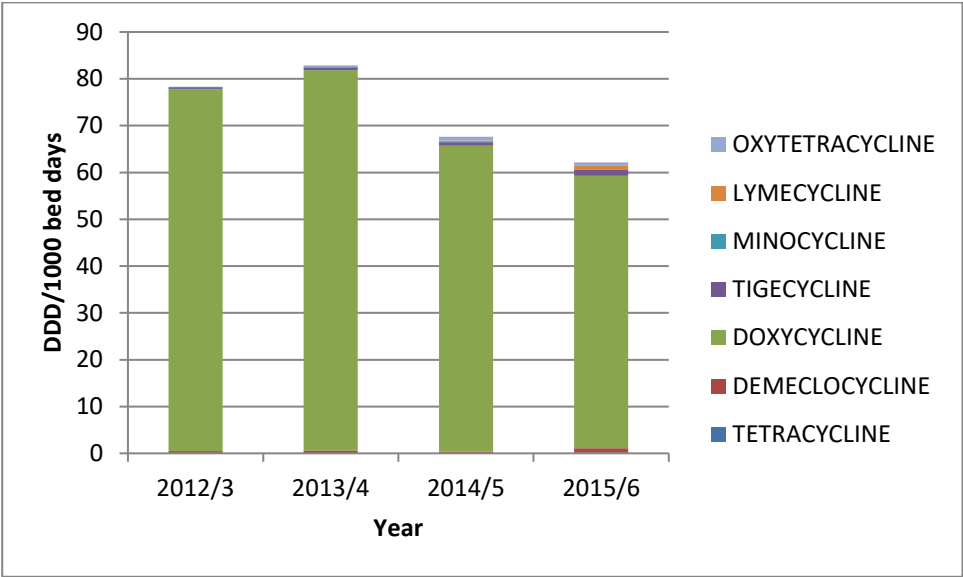
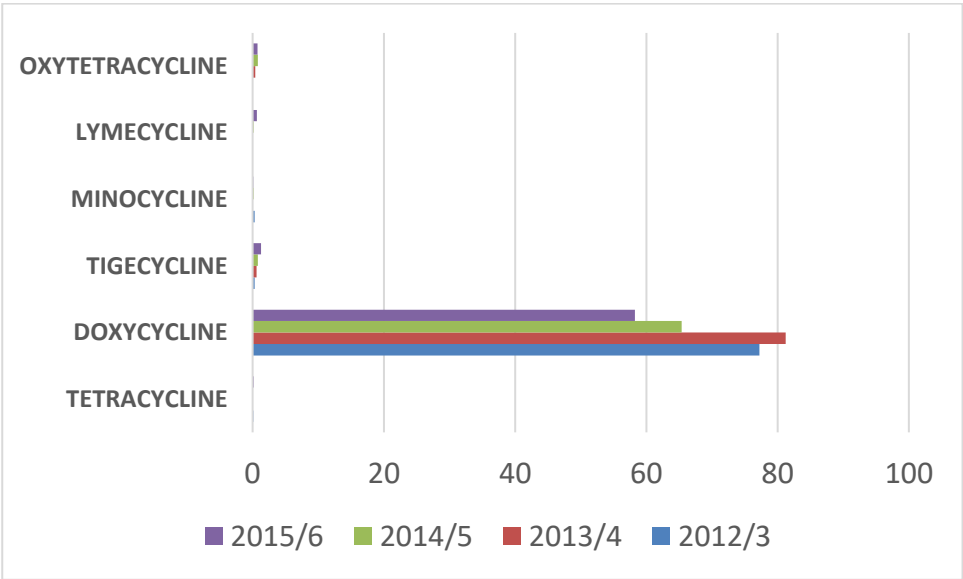
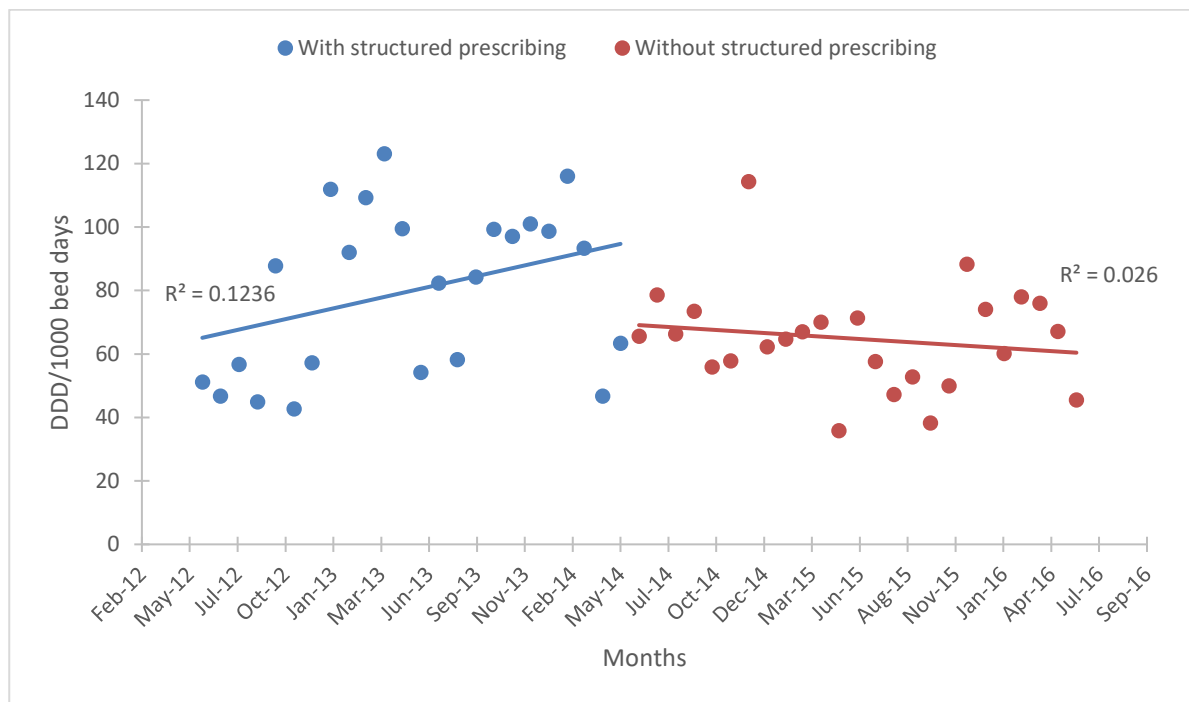


Figure 41: Tetracyclines consumption by group, expressed as DDD per 1000 bed days, 2012-2016



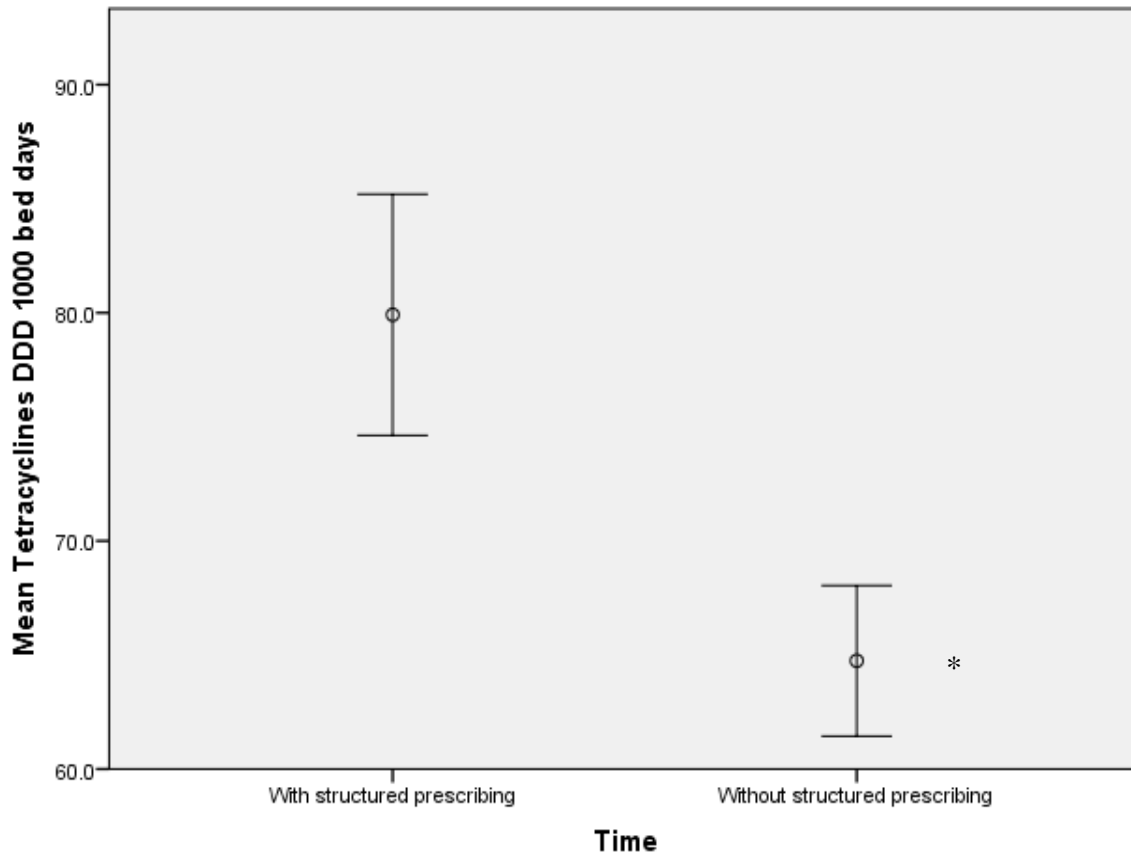
In figure 42, there was an increase in the use of tetracyclines in the period with structured prescribing and a decrease in use in the period without structured prescribing. There was a positive correlation between the variables for the period with structured prescribing ($R^2 = 0.1236$) and a weak negative correlation for the period without structured prescribing ($R^2 = 0.026$).

Figure 42: Monthly consumption of tetracyclines reported as DDD/1000 bed days. Trend lines established by linear regression before and after deployment of structured prescribing are shown



The mean difference and standard error bars shown in figure 43 for tetracyclines show a mean difference of 15.16 DDD/1000 bed days and is statistically significant ($p= 0.02$).

Figure 43: Mean difference for tetracyclines use for the periods with and without structured prescribing



Comparisons of means of DDD/1000 bed days of tetracyclines and standard error bars for the periods with and without structured prescribing

*indicates significant $p \leq 0.05$

5.5.3.3 Antimycobacterials

This class of antibiotics are used to treat infections with mycobacterium species. They are used for the treatment of tuberculosis and leprosy. Isoniazid, ethambutol, pyrazinamide and rifampicin are used for the treatment of tuberculosis. Dapsone and clofazimine are used for the treatment of leprosy (Public Health England, 2014).

The use of antimycobacterials decreased between June 2012 and June 2016 from 131 to 121.4 DDD per 1000 bed days. Rifampicin was the most commonly used antimycobacterials and accounted for 35 % of all antimycobacterials used.

Figure 44: Consumption of antimycobacterials, expressed as DDD per 1000 bed days, 2012-2016

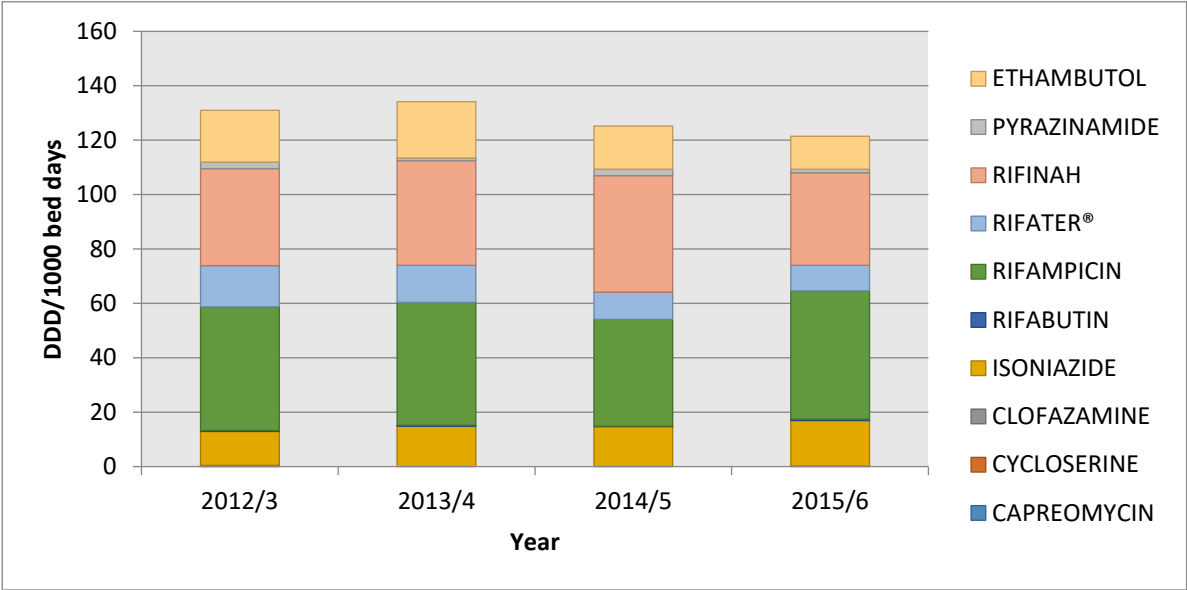


Figure 45: Antimycobacterials consumption by group, expressed as DDD per 1000 bed days, 2012-2016

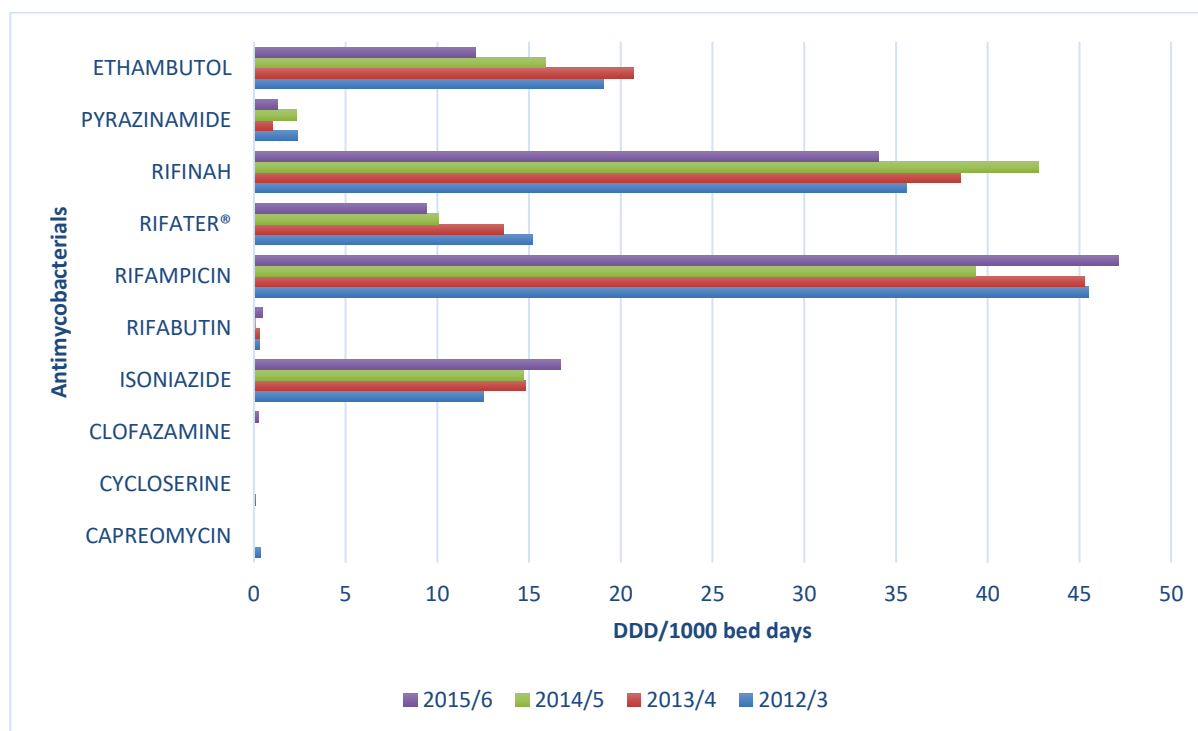
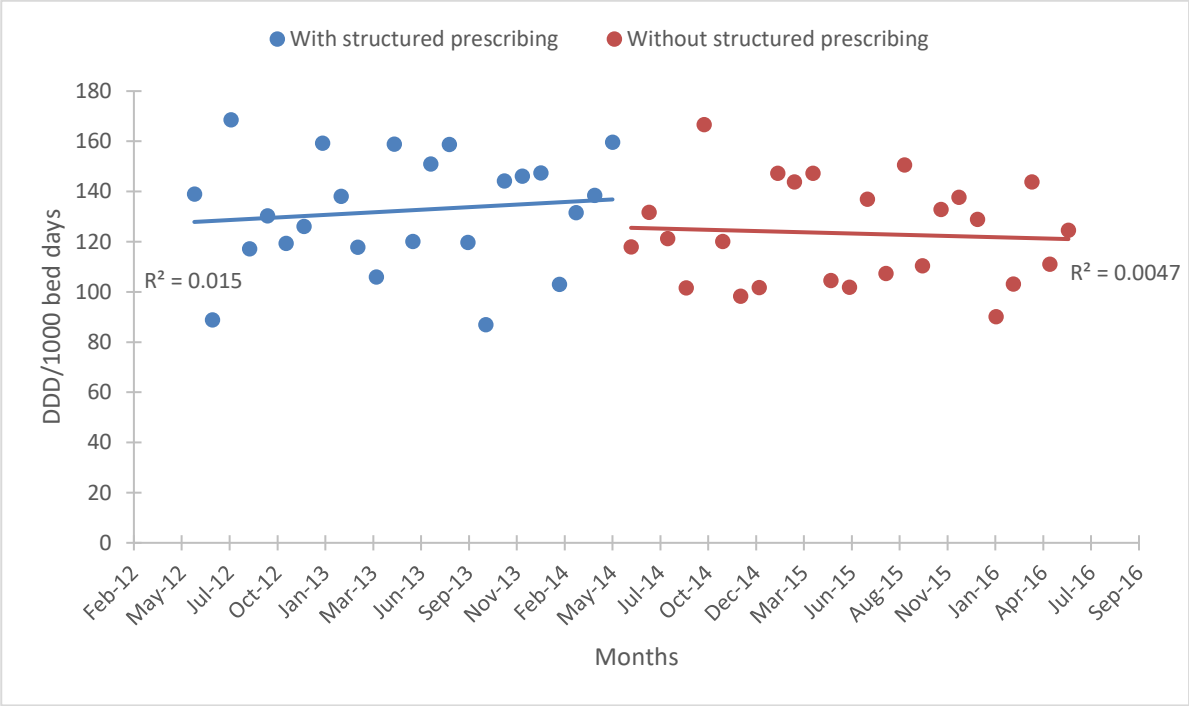


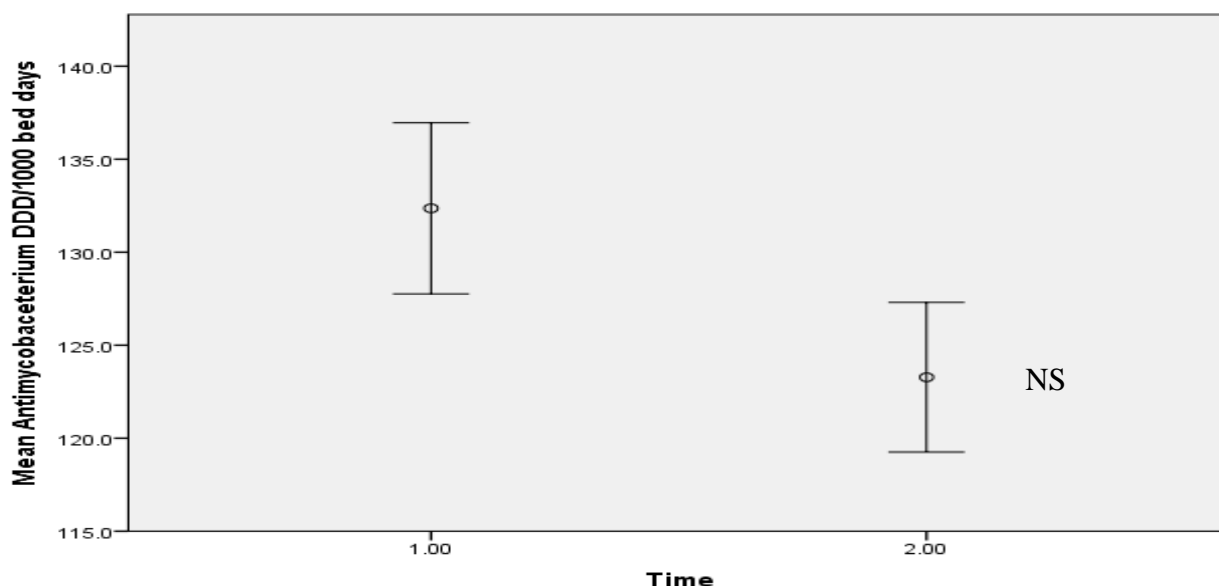
Figure 46 shows an increase in the use of antimycobacterials in the period with structured prescribing and slight reduction in the period without structured prescribing. There was a weak positive correlation between the variables for the period with structured prescribing ($R^2= 0.015$) and a weak negative correlation between the variables for the period without structured prescribing ($R^2=0.0047$).

Figure 46: Monthly consumption of antimycobacterials reported as DDD/1000 bed days. Trend lines established by linear regression before and after deployment of structured prescribing are shown



The mean difference and standard error bars shown in Figure 47 for antimycobacterials show a mean difference of 9.08 DDD/1000 bed days but this difference is not statistically significant $p=0.143$

Figure 47: Mean difference for antimycobacterials use for the periods with and without structured prescribing



Comparisons of means of DDD/1000 bed days for antimycobacterials and standard error bars for the periods with and without structured prescribing

NS indicates not significant

5.5.4 Antibiotics where structured prescribing is associated with no change in their use

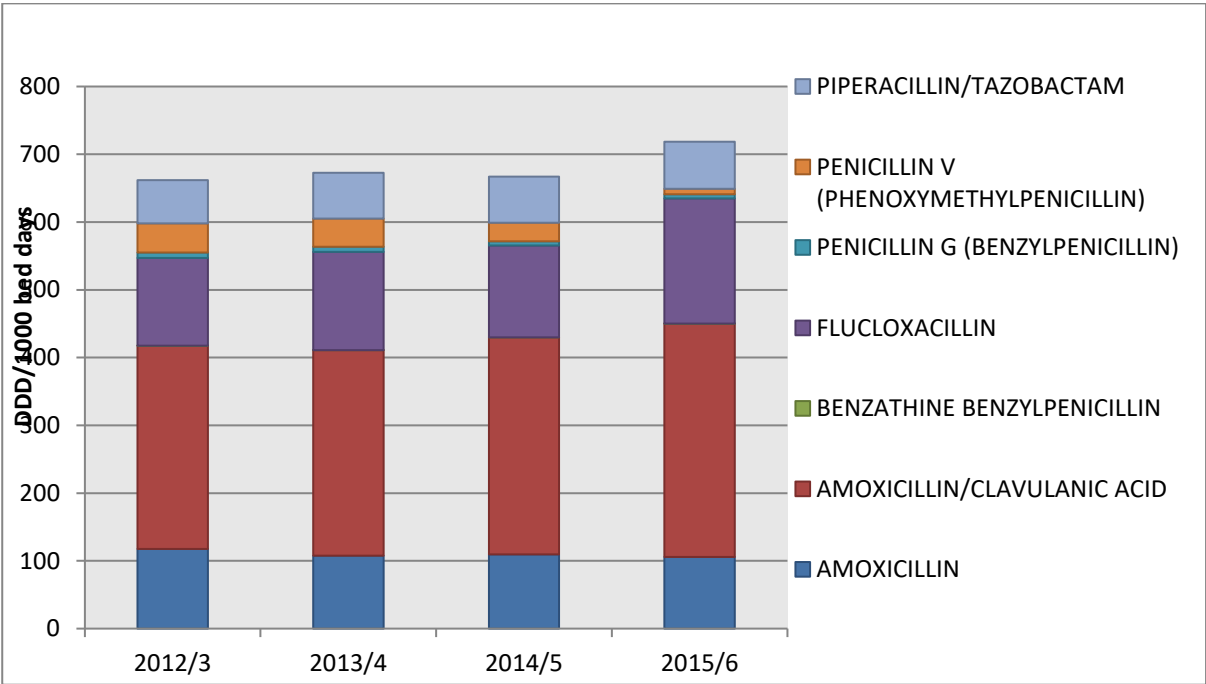
5.5.4.1 Penicillins

This class of antibiotics are active against a wide range of Gram-positive and Gram-negative bacteria. Flucloxacillin is mainly used for infections caused by staphylococci and is also recommended for the treatment of impetigo and cellulitis (Public Health England, 2014). Amoxicillin is recommended for the treatment of upper and lower respiratory tract infections (Public Health England, 2014). Phenoxymethyl penicillin is recommended for the treatment of non-viral sore throat (Public Health England, 2014). Some penicillins are combined with β -lactamase inhibitors such as co-amoxiclav and piperacillin-tazobactam to produce broad spectrum antibiotics and used to treat infections caused by Gram-positive and Gram-negative bacteria and anaerobes (Public Health England, 2014). These combination products are effective in treatment of sepsis and intraabdominal infections. Piperacillin-

tazobactam and co-amoxiclav are replacing cephalosporins and quinolones for empirical treatment of infections (Public Health England, 2014).

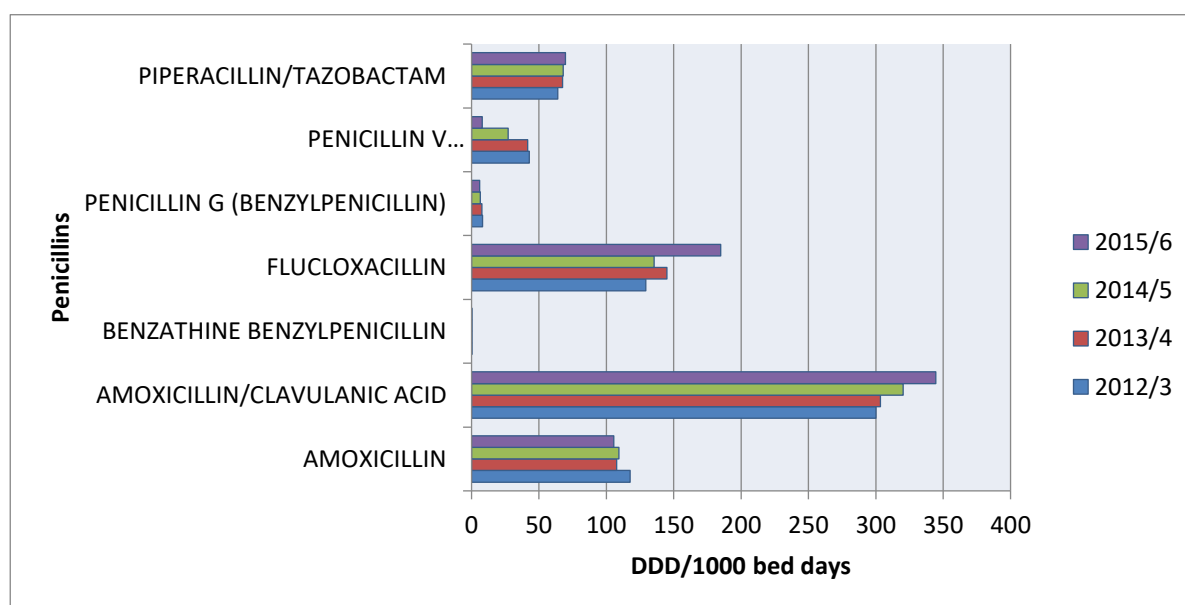
Penicillins accounted for almost 45% of total antibiotic consumption at UHBFT over the four-year period. Between June 2012 and June 2016 there was a 18% increase in total consumption of this group from 7925.28 to 9350.63 DDD per 1000 bed days.

Figure 48: Consumption of penicillins, expressed as DDD per 1000 bed days, 2012-2016



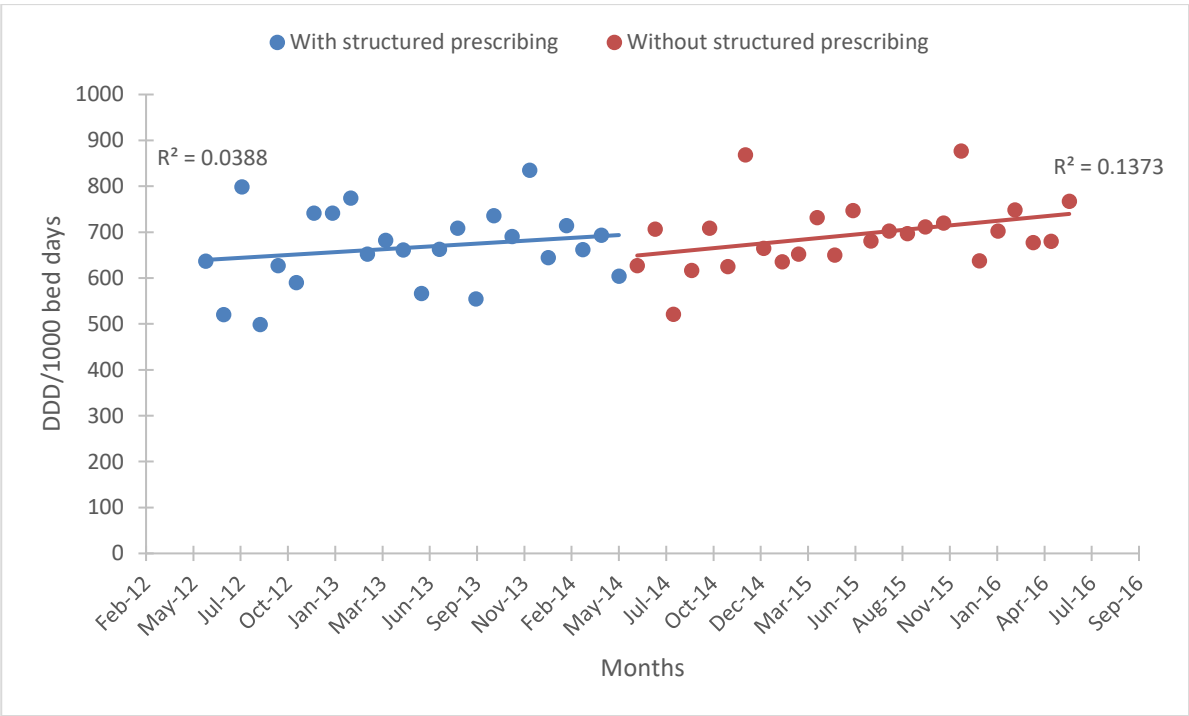
The top seven most commonly used penicillins are presented in Figure 49. Co-amoxiclav was the most commonly used penicillin (47% of all penicillins used). Co-amoxiclav use increased from 300.087 to 344.565 DDD per 1000 bed days between June 2012 to June 2016 (an increase of 14.8%). Piperacillin-tazobactam use increased from 64.08 to 69.63 DDD per 1000 bed days between June 2012 and June 2016 (an increase of 8.7%).

Figure 49: Penicillins consumption by group, expressed as DDD per 1000 bed days, 2012-2016



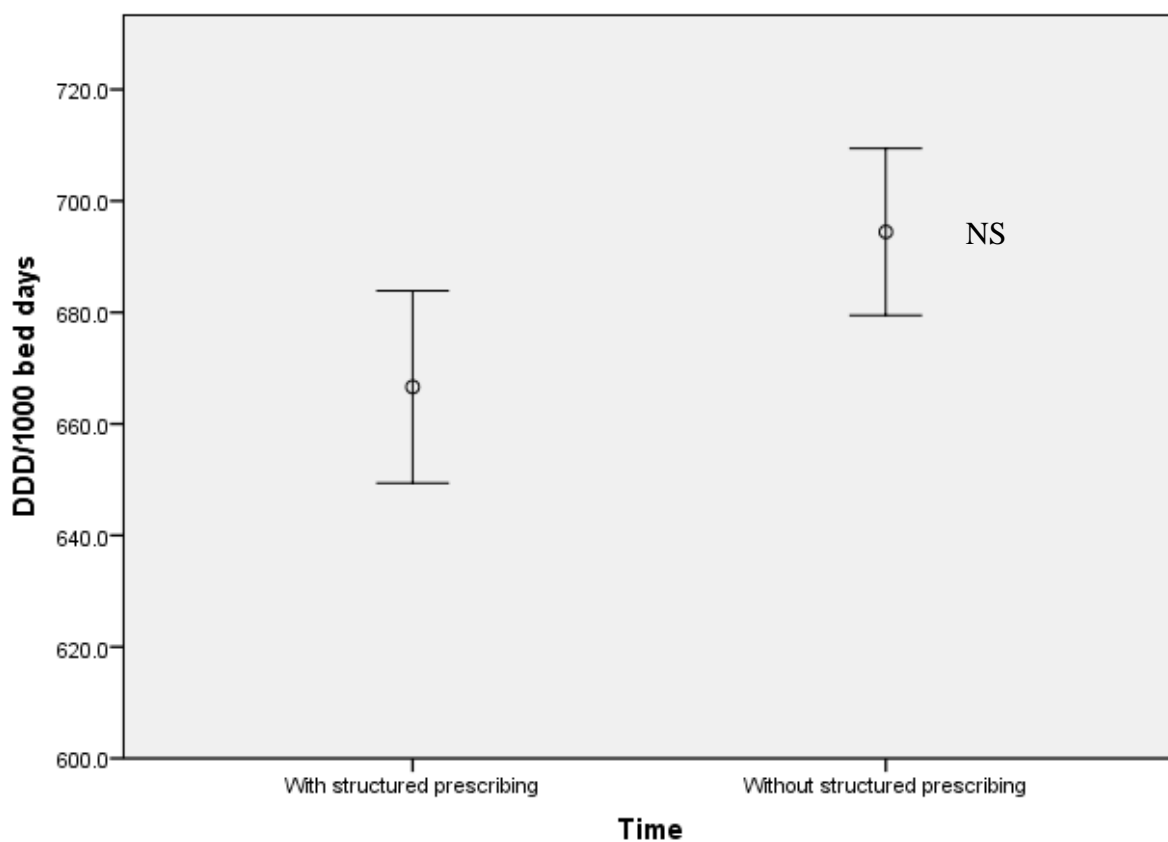
In figure 50, there was an increase in the use of penicillins in both periods with and without structured prescribing. There was a weakly positive correlation between the variables for both periods with structured prescribing ($R^2= 0.0388$) and without structured prescribing ($R^2=0.1373$).

Figure 50: Monthly consumption of penicillins reported as DDD/1000 bed days. Trend lines established by linear regression before and after deployment of structured prescribing are shown



The mean difference and standard error bars shown in figure 51 for penicillins show no difference in mean of the total usage of antibiotics in the period with structured prescribing compared to the period without structured prescribing due to overlapping error bars. There was a mean difference on -27.8 DDD/1000 bed days but this was not statistically significant ($p= 0.229$).

Figure 51: Mean difference for penicillins use for the periods with and without structured prescribing



Comparison of means of DDD/1000 bed days of penicillins with standard error bars with and without structured prescribing

NS indicates not significant

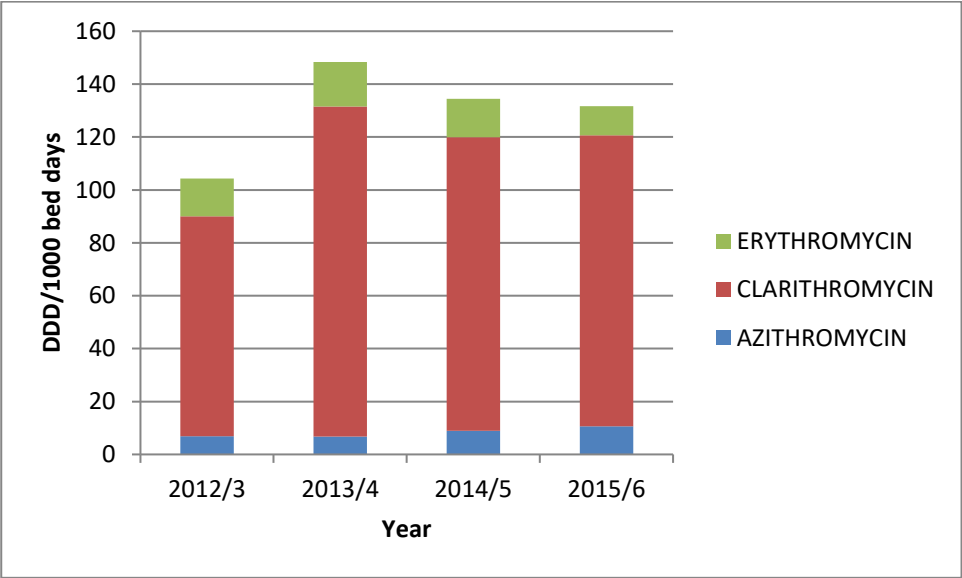
5.5.4.2 Macrolides

This class of antibiotics is active against Gram-positive and Gram-negative bacteria. They exert their action by inhibiting bacterial protein synthesis. Clarithromycin is recommended for the treatment of upper and lower respiratory tract infections (Public Health England, 2014). This group of antibiotics

is also used as part of the triple therapy for the treatment of *Helicobacter pylori* infections and for the treatment of *Chlamydial* genital infections (Public Health England, 2014).

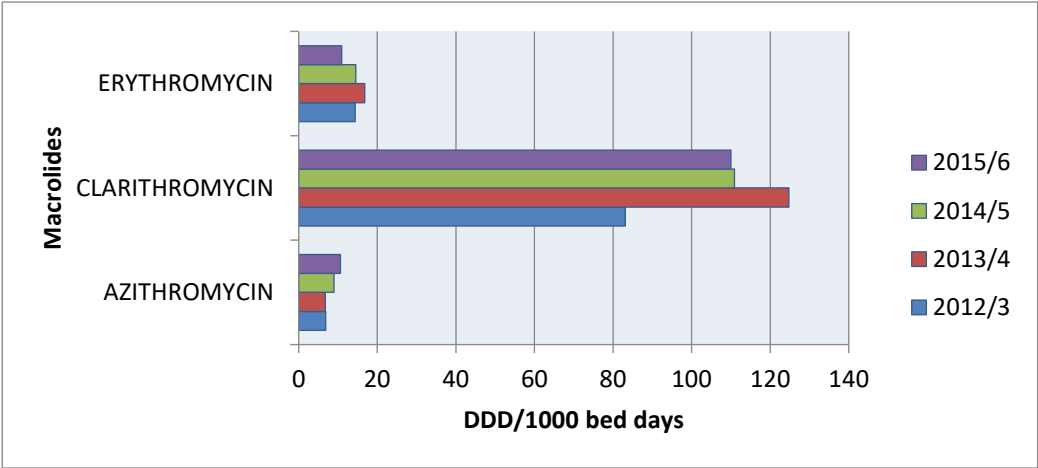
The use of macrolides increased between June 2012 and June 2016 from 104.3 to 131.6 DDD per 1000 bed days (an increase of 26.2%). The increase in the use macrolides most predominantly occurred between June 2012/3 to June 2013/4 from 104.3 to 148.3 DDD per 1000 bed days.

Figure 52: Consumption of macrolides, expressed as DDD per 1000 bed days, 2012-2016



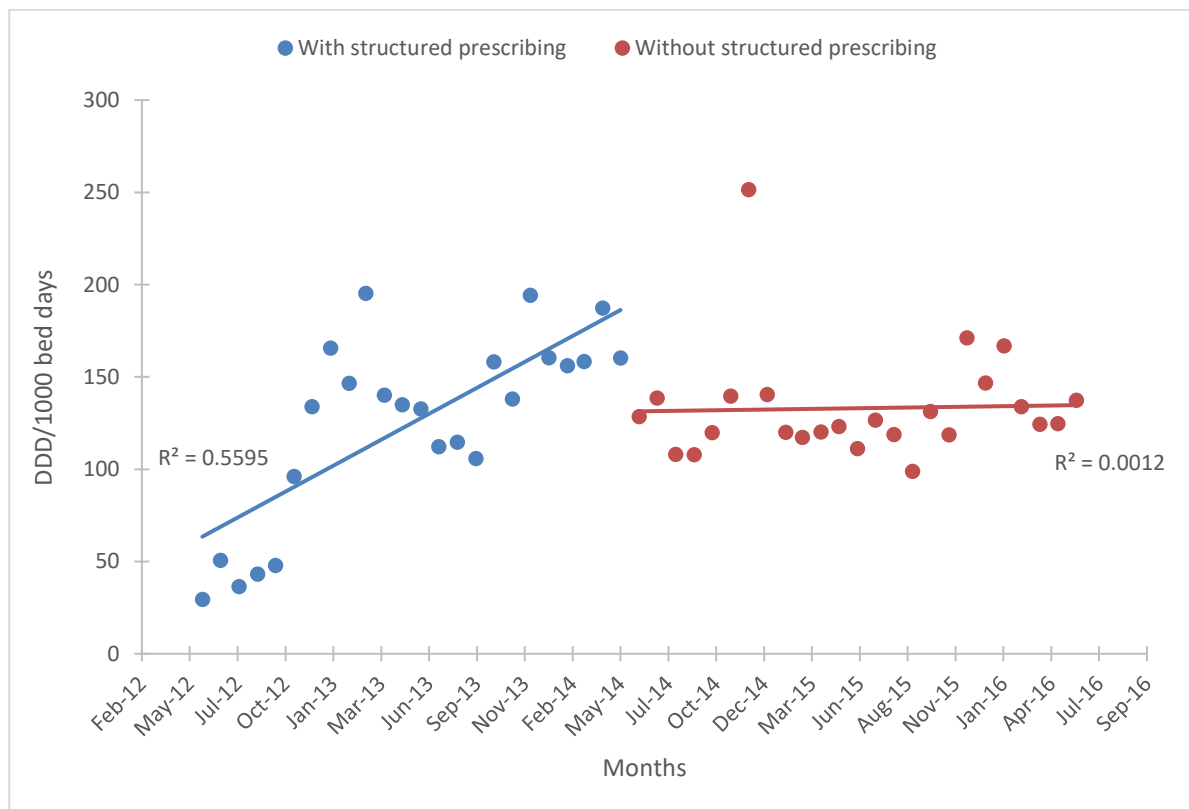
Clarithromycin was the most commonly used macrolide and accounted for 83% of all macrolides used. The use of clarithromycin increased between June 2012 and June 2016 from 83.1 to 110 DDD per 1000 bed days (an increase of 32.4%). The use of azithromycin increased by 53.6% and the use of erythromycin decreased by 23% over the same period.

Figure 53: Macrolides consumption by group, expressed as DDD per 1000 bed days, 2012-2016



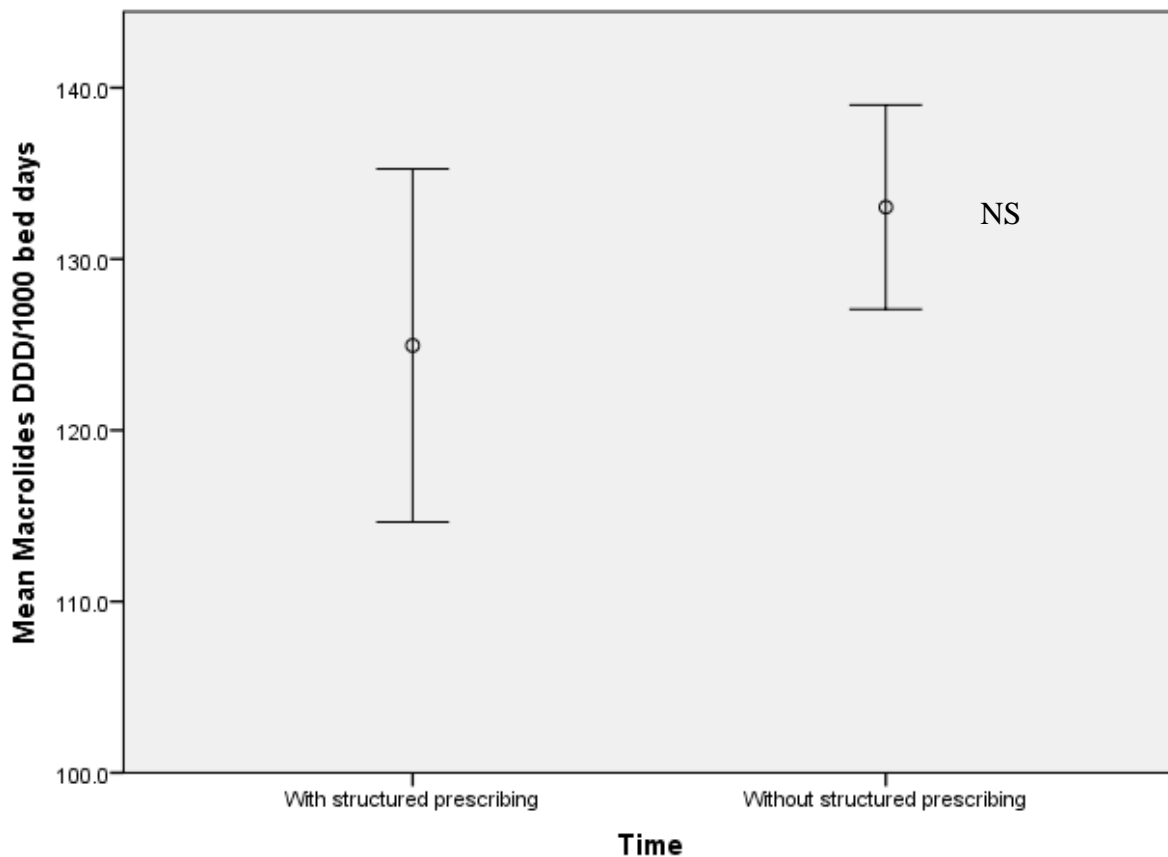
In figure 54, there was an increase in the use of macrolides in the period with structured prescribing and no change in the period without structured prescribing. There was a moderate positive correlation between the variables for the period with structured prescribing ($R^2 = 0.5595$) and neutral weak correlation between the variables for the period without structured prescribing ($R^2 = 0.0012$).

Figure 54: Monthly consumption of macrolides reported as DDD/1000 bed days. Trend lines established by linear regression before and after deployment of structured prescribing are shown



The mean difference and standard error bars shown in Figure 55 for macrolides show a mean difference of -8.07 DDD/1000 bed days but this difference was not statistically significant ($p=0.502$).

Figure 55: Mean difference for macrolides use for the periods with and without structured prescribing



Comparisons of means of DDD/1000 bed days of Macrolides and standard error bars for the periods with and without structured prescribing

NS indicates not significant

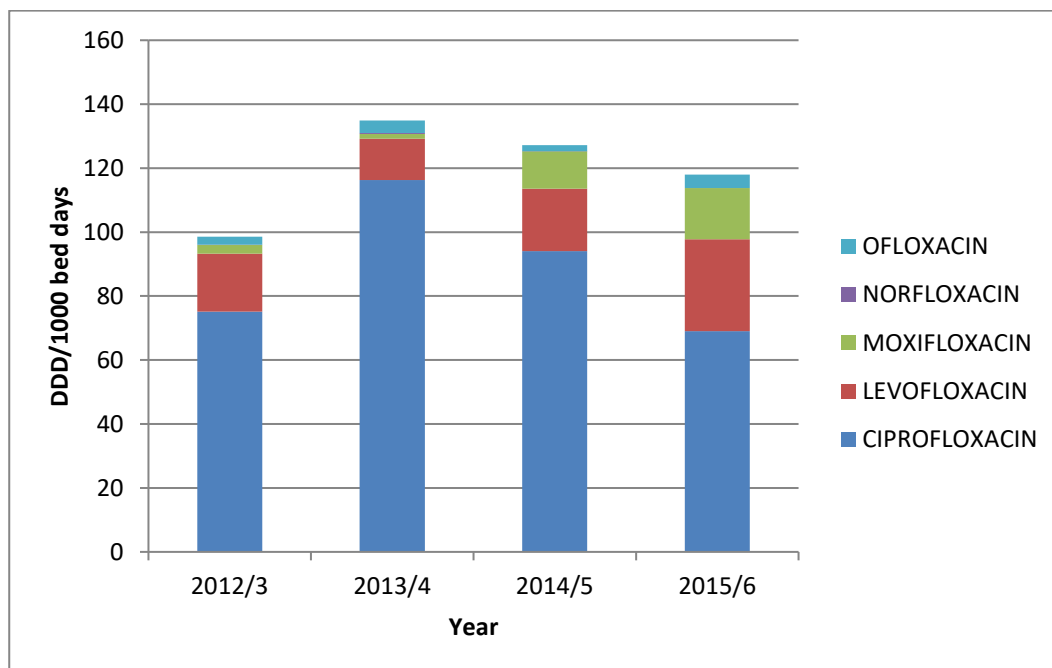
5.5.4.3 Quinolones

This class of antibiotics was developed in the 1960s. They are broad-spectrum antibiotics and active against Gram-positive and Gram-negative bacteria. They have been mainly used for treating community acquired pneumonia and urinary tract infections (Public Health England, 2014). Given their excellent oral bioavailability, they are administered orally more often than parenterally (Public Health England, 2014). The use of quinolones has been associated with an increase in *Clostridium difficile* and *Staphylococcus* infections by disrupting the normal flora of the gut. Ciprofloxacin in

recommended for the treatment of urinary tract infections such as pyelonephritis and acute prostatitis (Public Health England, 2014).

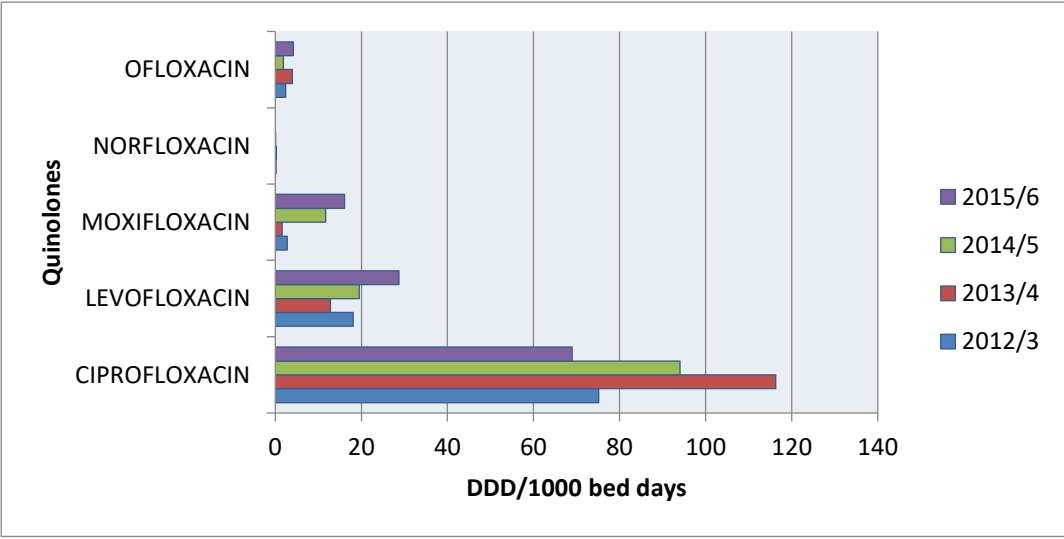
The use of quinolones increased from 98.5 to 118 DDD per 1000 bed days between June 2012 and June 2016 (an increase of 20%). The increase in use of quinolones occurred mainly between June 2012/3 and June 2013/4 from 98.5 to 135 DDD per 1000 bed days (an increase of 37%). This was then followed by a decrease in use from 135 to 127 DDD per 1000 bed days between the periods June 2013/4 and June 2014/5 (a decrease of 6%).

Figure 56: Consumption of quinolones, expressed as DDD per 1000 bed days, 2012-2016



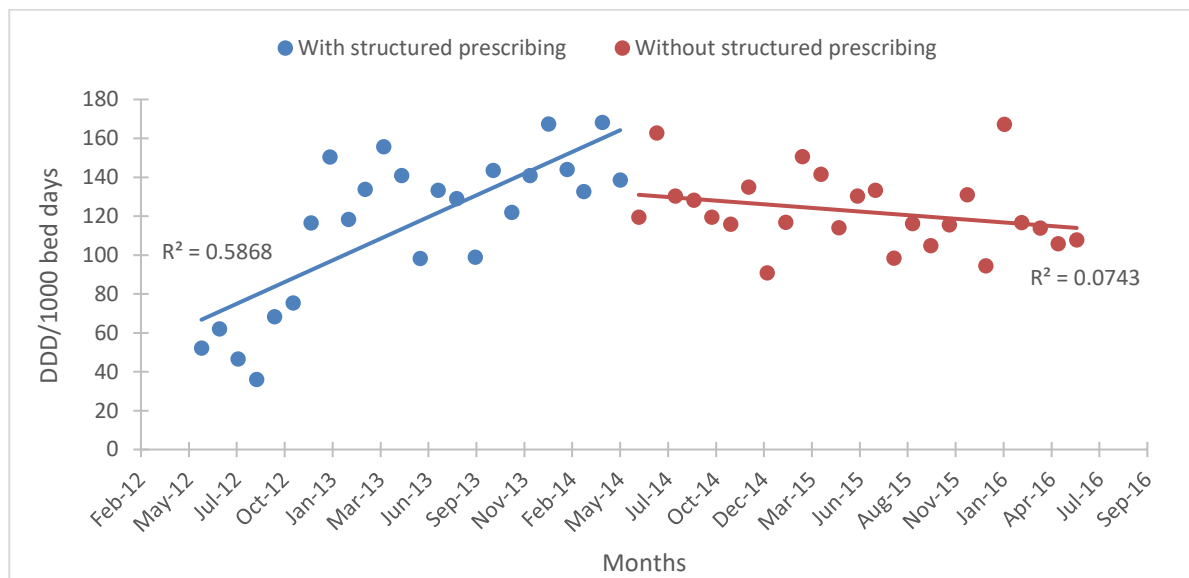
Ciprofloxacin was the most commonly used quinolone and accounted for 76% of all quinolones used. The use of ciprofloxacin first increased from 75.1 to 116.3 DDD per 1000 bed days between June 2012/3 and June 2013/4 and then decreased to 94 and 69 DDD per 1000 bed days in June 2014/5 and June 2015/6, respectively. The use of ciprofloxacin decreased due to *Clostridium difficile* infections.

Figure 57: Quinolones consumption by group, expressed as DDD per 1000 bed days, 2012-2016



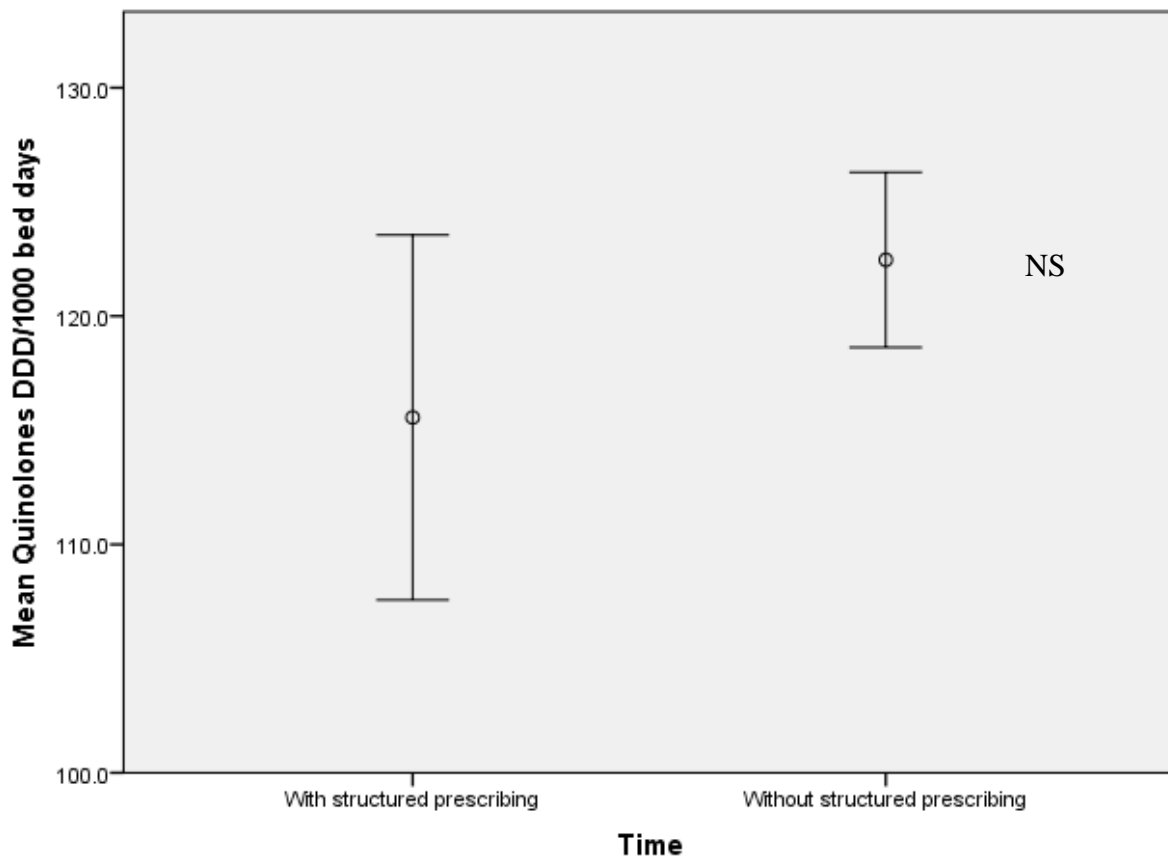
In Figure 58, there was an increase in the use of quinolones in the period with structured prescribing and no change in the period without structured prescribing. There was a moderate positive correlation between the variables for the period with structured prescribing ($R^2 = 0.5868$) and negative weak correlation between the variables for the period without structured prescribing ($R^2 = 0.0743$).

Figure 58: Monthly consumption of quinolones reported as DDD/1000 bed days. Trend lines established by linear regression before and after deployment of structured prescribing are shown



The mean difference and standard error bars shown in Figure 59 for quinolones show a mean difference of -6.9 DDD/1000 bed days but this difference was not statistically significant $p=0.441$.

Figure 59: Mean difference for quinolones use for the periods with and without structured prescribing



Comparisons of means of DDD/1000 bed days of quinolones and standard error bars for the periods with and without structured prescribing
NS indicates not significant

5.5.4.4 Miscellaneous antibiotics

This group of antibiotics contains agents with different mechanisms of activity. Examples include linezolid, daptomycin and quinprostin-dalfoprostin which are used for the treatment of infections with resistant Gram-positive bacteria. Metronidazole is used for the treatment of infections caused by clostridia spp, parasitic infections and infections caused by a variety of anaerobes. Chloramphenicol is used for the treatment of fever caused by salmonella and for the management of severe meningitis

and acute exacerbation of COPD. Colisitin contains polymixins and is used to treat infections caused by *Pseudomonas aeruginosa* (Public Health England, 2014) .

The use of miscellaneous antibiotics as a whole remained stable over the four-year period changing from 145.1 to 146.2 DDD per 1000 bed days. The most commonly used antibiotic among this group was metronidazole which accounted for 35% of all miscellaneous antibiotics used. The use of metronidazole decreased over the four-year period from 58.3 to 44.1 DDD per 1000 bed days .

Figure 60: Consumption of miscellaneous, expressed as DDD per 1000 bed days, 2012-2016

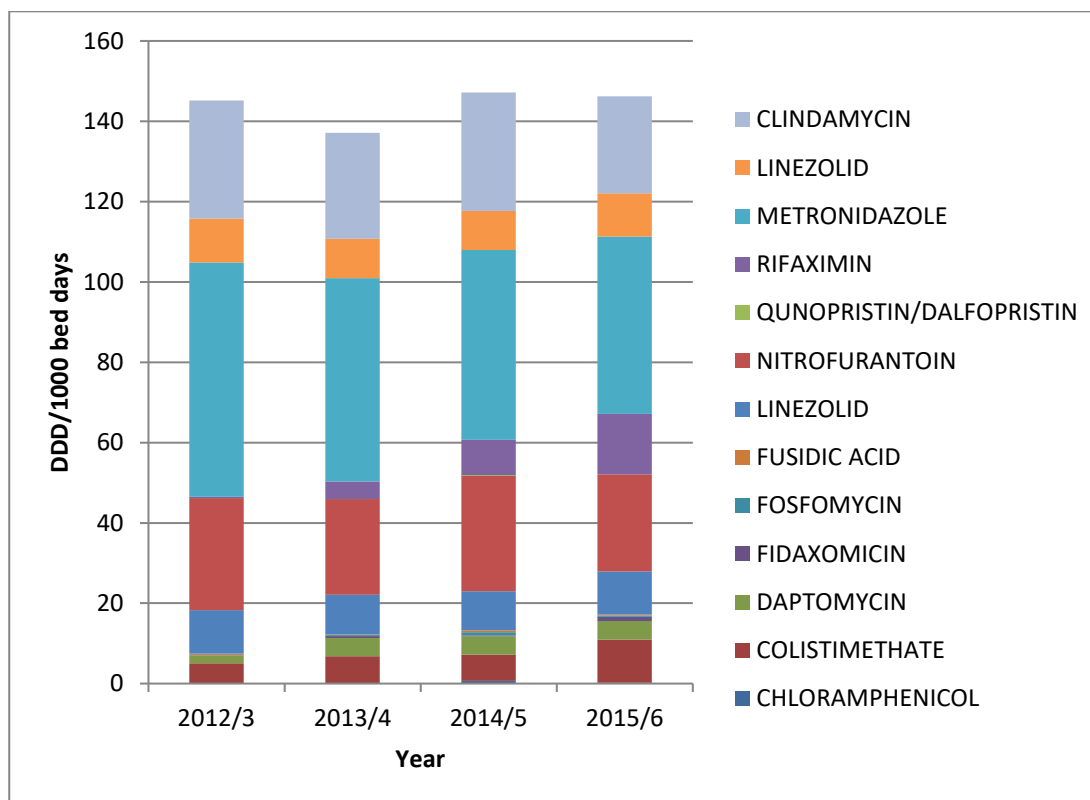
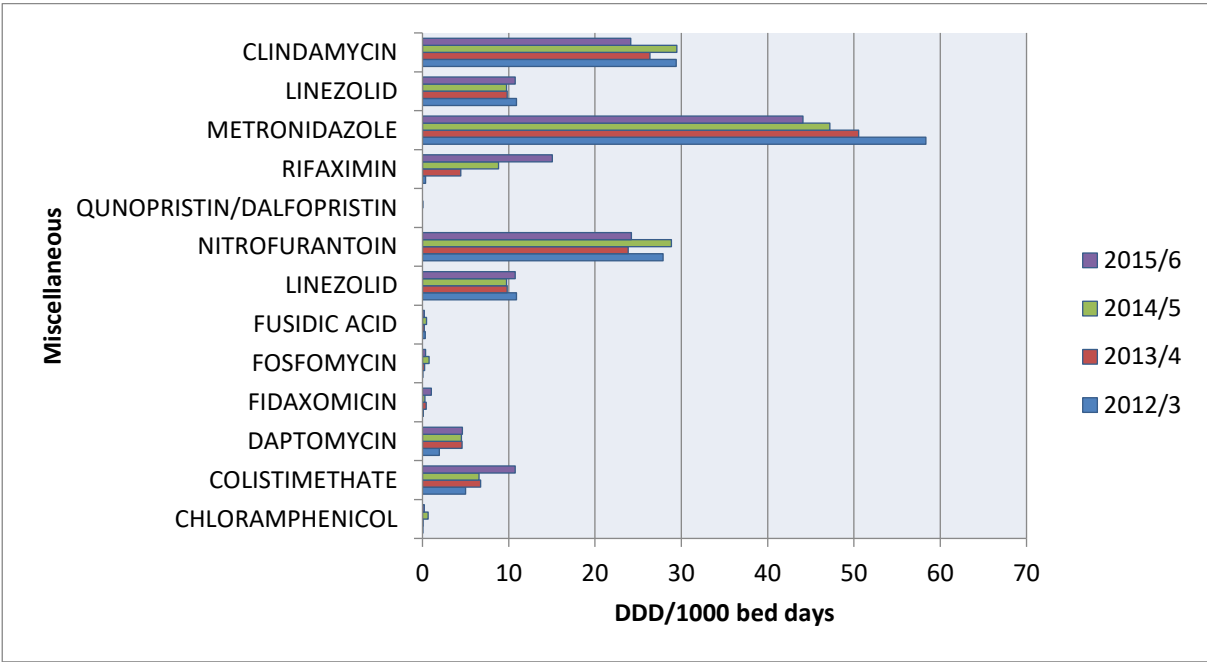
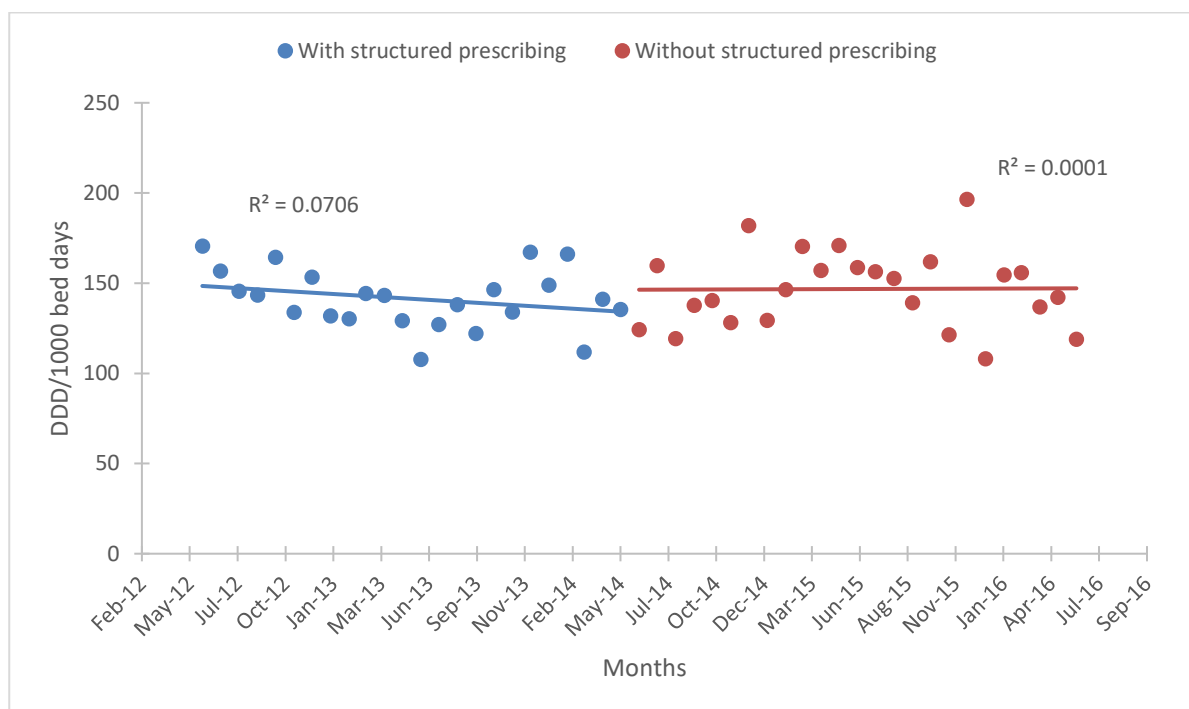


Figure 61: Miscellaneous consumption by group, expressed as DDD per 1000 bed days, 2012-2016



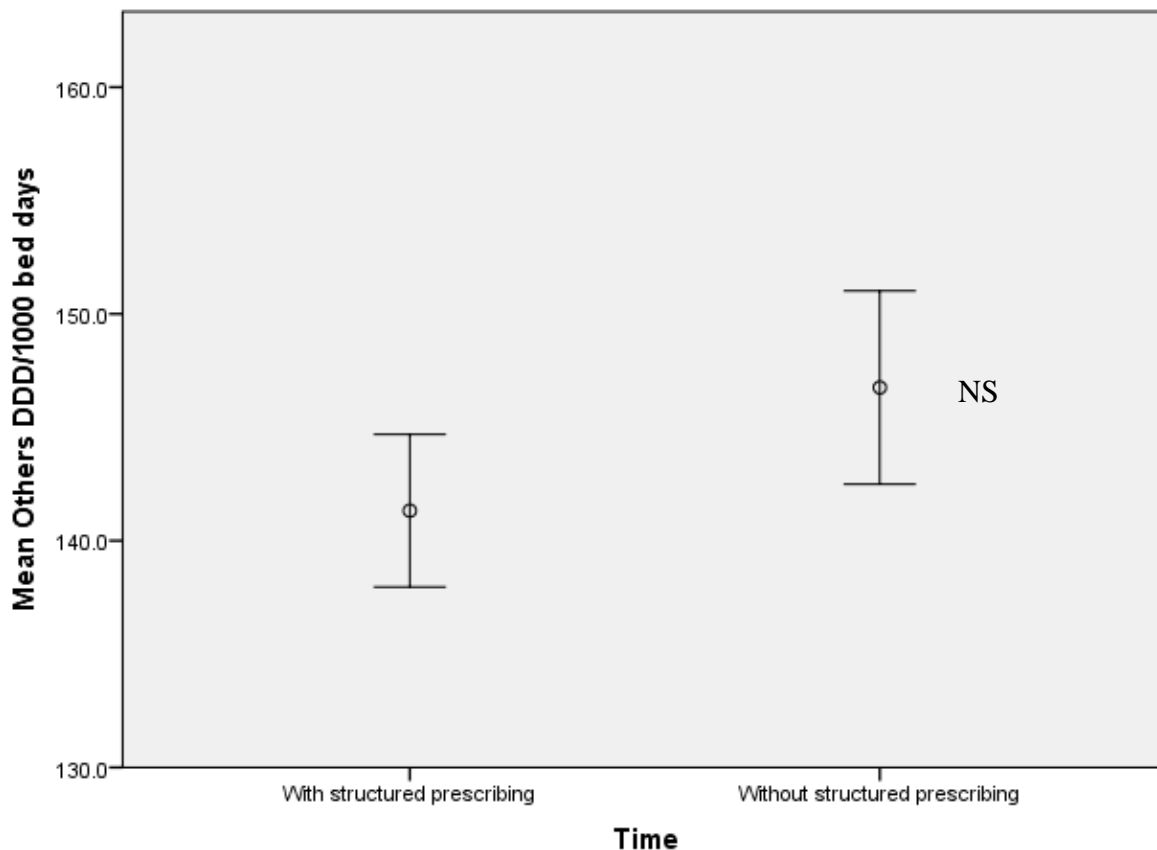
In Figure 62, there was a slight reduction in the use of miscellaneous antibiotics in the period with structured prescribing and no change in the period without structured prescribing. There was a weak neutral correlation between the variables for the period with structured prescribing ($R^2 = 0.0706$) and without structured prescribing ($R^2 = 0.0001$).

Figure 62: Monthly consumption of other ABXs reported as DDD/1000 bed days. Trend lines established by linear regression before and after deployment of structured prescribing are shown



The mean difference and standard error bars shown in Figure 63 for miscellaneous antibiotics show that there was a mean difference of -5.43 DDD/1000 bed days but this difference was not statistically significant ($p=0.325$).

Figure 63: Mean difference for miscellaneous use for the periods with and without structured prescribing



Comparisons of means of DDD/1000 bed days of other antibiotics and standard bar errors for the periods with and without structured prescribing

NS indicates not significant

5.6 Discussion

It can be seen from the results presented that structured prescribing may influence the use of antibiotics. Total antibiotic consumption measured as DDD/1000 bed-days increased each year between 2012 and 2016. The two groups of antibiotics most predominantly prescribed were

penicillins and macrolides. There was significant variability in both total antibiotic use and the use of different antibiotics over time at UHBFT.

UHBFT prescribing guidelines delivered via the PICS CDSS may influence the consumption of antibiotics. This is evidenced by the lower consumption of cephalosporins and carbapenem in the period with structured prescribing compared to the period without structured prescribing. The lower consumption of cephalosporins and carbapenems in the period with structured prescribing was to be expected as a number of national initiatives at that time focused on reducing the numbers of *C. difficile* infections (CDI) (2008). There were local and national plans for CDI reduction which were mandatory and UHBFT must implement solutions to achieve and it has sought to meet these by addressing the use of antibiotic classes particularly associated with the selection of *C. difficile*, such as cephalosporins and carbapenems.

When there is a decrease in the use of one class of antibiotics, there is often a compensatory increase in the use of other antibiotics. This phenomenon is called ‘squeezing the balloon’ (Peterson, 2005). In the case of UHBFT, increased use of penicillins, macrolides and quinolones was observed in the period with structured prescribing. These changes could have adverse consequences for patient care as there is a worldwide concern about spread of resistant microorganisms to broad spectrum antibiotics such as β -lactamase and carbapenemase resistant bacteria. The relative changes of each agent used at UHBFT need to be interpreted with caution as an increase in one group may lead to a reduction in another group of antibiotics where an alternative agent is used for the same indication. There was a reduction in the use of sulfonamides during the period with structured prescribing and marked increase in the use of sulfonamides when structured prescribing was taken out. The use of sulfonamides was mainly driven by sulfasalazine which is not prescribed as an antibiotic. Sulfasalazine is used to treat Crohn’s disease.

A 'before and after' study conducted in Brazil examined the impact of CDSS on the volume of cefazolin used and its cost (Okumura et al., 2016). The study showed that CDSS reduced cefazolin use from 6.31 to 2.15 DDD/100 bed-days ($p < 0.05$), and provided a cost saving of USD 50,433.39 over the period studied. CDSS has been shown to be successful in reducing the volume of antibiotic use from 167 to 149 DDD/100 ICU bed-days (Thursky et al., 2006). The study differed from the present work in that the impact of CDSS on the consumption of broad-spectrum antibiotics in ICU setting was evaluated whereas the present study evaluated the impact of CDSS on a whole hospital and covered all antibiotics. Another study showed that use of CDSS decreased the volume of antibiotic use from 1,767 DDD to 1,458 DDD per 1,000 patient-days ($p = 0.04$) (Sintchenko et al., 2005). This study differed from the current study in that they evaluated other outcomes such as mortality and length of stay.

The slope of the trend lines of antibiotic consumption varied during the periods with and without structured prescribing. For all antibiotics, the slope of the trend line for the period with structured prescribing was steeper than the slope of the trend line for the period without structured prescribing. This could mean that structured prescribing encouraged the use of antibiotics due to a hospital policy and that would be an indication of a positive influence of structured prescribing on antibiotic consumption. This may have caused the trend line to look steeper during the period with structured prescribing than without it. However, for both of the years when CDSS was in place the total antibiotic use was at a lower level than without it. Antibiotic usage as measured by DDD per 1000 bed days was lower with CDSS. For cephalosporins, the trend line for the period with structured prescribing had a positive slope. The trend line of cephalosporin consumption for the period without structured prescribing had a negative slope. This could mean that structured prescribing encouraged the use of cephalosporin due to hospital policy during the period with structured prescribing. However, when CDSS was in place the total cephalosporin use for both of the years was lower with

CDSS than without it. For carbapenems, the trend line for carbapenems consumption during the period with structured prescribing had a negative slope compared to the trend line of carbapenems consumption during the period without structured prescribing which had a positive slope. This could mean that structured prescribing was successful in reducing the use of broad spectrum antibiotics such as carbapenems. Carbapenems usage as measured by DDD per 1000 bed days was lower with CDSS. For glycopeptides, the slope of the trend line of glycopeptide consumption during the period with structured prescribing was steeper than the slope of the trend line of glycopeptide consumption during the period without structured prescribing. The trend line of glycopeptide consumption went up during the period with structured prescribing. This could mean that structured prescribing encouraged the use of glycopeptides due to hospital policy during the period with structured prescribing for treating severe infections such as *Clostridium difficile*. Glycopeptide usage as measured by DDD per 1000 bed days was lower with CDSS. For aminoglycosides, the slope of the trend line of aminoglycosides consumption during the period with structured prescribing was steeper than the slope of the trend line of aminoglycosides consumption during the period without structured prescribing. The trend line for aminoglycoside consumption went up during the period with structured prescribing. This could mean that structured prescribing encouraged the use of aminoglycoside due to hospital policy during the period with structured prescribing. When CDSS was in place the total aminoglycoside use for both of the years was higher with CDSS than without it. Streptomycin is used as an antimycobacterial unlike other aminoglycosides. For penicillins, both trend lines of penicillin consumption during the periods with and without structured prescribing had a positive slope, however, the slope of the trend line for period without structured prescribing was slightly steeper than the slope of the trend line for the period with structured prescribing. This could mean that structured was successful in reducing the use of penicillin during the period with structured prescribing. When CDSS was in place the total penicillin use for both of the years was lower with CDSS than without

it. The slope of these trend lines could be influenced by many factors apart from structured prescribing such as seasonality changes, epidemics, staff turn-over and case-mix. For some antibiotics, structured prescribing was associated with reduction of antibiotic use such as sulfonamides and carbapenems. For others, structured prescribing was associated with increase of antibiotic use such as tetracyclines, aminoglycosides, and macrolides.

Structured prescribing was associated with changes in the patterns of consumption of broad spectrum antibiotics. Structured prescribing was associated with increase in the use of narrow spectrum antibiotics. For example, structured prescribing was associated with reduced use of cephalosporins and carbapenems. Ceftriaxone use increased but the use of other cephalosporins decreased. This has led to an increased use of other antibiotics such as aminoglycosides and tetracyclines. Structured prescribing may have influenced the use of aminoglycosides over penicillins or cephalosporins. Tetracyclines was prescribed as an alternative treatment to carbapenems or cephalosporins. For mild cases of infection, structured prescribing preferred prescribing narrow spectrum antibiotics such as tetracyclines over broad spectrum antibiotics evident by the reduced use of cephalosporins, quinolones and carbapenems.

Prescribing narrow spectrum antibiotics and avoiding broad spectrum antibiotics was the main aim of structured prescribing. There were other factors that may have influenced the way structured prescribing worked. Junior doctors were strongly influenced by their superiors in prescribing broad-spectrum antibiotic for severe cases on infection. There is a possibility that that there were severe cases of infection that required the use of broad spectrum antibiotic and overriding structured prescribing recommendations. For example, in patients with meningitis broad spectrum antibiotics need to be prescribed as early as possible. Clinicians may have found structured prescribing recommendations for treating meningitis not suitable and that is why they overlooked structured

prescribing recommendations. Clinicians have their own experience in treating severe infections and maybe their experience conflicted with structured prescribing recommendations.

Staff turn-over is one of the factors that may have influenced the way structured prescribing worked. The lack of adequate training may have made some staff unaware of the presence of structured prescribing. Training sessions may have been at fixed terms and some staff may have missed these training sessions. Clinicians who may have missed these training sessions were unaware of the decision support functionality of structured prescribing and that is why they overruled structured prescribing recommendations.

Cost of antibiotics is one of the factors that may have influenced the way structured prescribing worked. Structured prescribing recommendations may have been tailored to prescribing cheaper antibiotics and avoiding expensive ones. Route of administration is another factor that may have influenced the way structured prescribing worked. Structured prescribing may have favoured prescribing oral antibiotics for mild infections and intravenous antibiotics for severe infections. Structured prescribing influenced the intravenous-oral conversion of antibiotics complying with antimicrobial stewardship strategies.

The current study has a number of limitations including that it was conducted at a single site and evaluated the impact of a single locally developed CDSS. A recommended method for evaluating antibiotic consumption is to use time series analysis. However, the use of DDDs over a short period of time to measure change may be potentially misleading as it does not take into account other factors influencing antibiotic use such as seasonality, staff changes, epidemics, new guidance and case mix.

Further research should include multisite studies evaluating more than one CDSS and include a wider population. There are a number of well-developed electronic prescribing systems with decision

support functionality and the conduct of multisite study comparing structured prescribing between CDSS will increase the strength of evidence and the validity of the findings from the current work.

Chapter 6: Exemplars of antibiotic consumption

In this section, the consumption of exemplar antibiotics and their trends of use at the study site are discussed. The following antibiotics were chosen because they are among the most commonly prescribed antibiotics in each class or there are problems with treatment resistant organisms. The mean difference for the use of each of the antibiotics between the periods with and without structured prescribing is discussed together with a regression analysis for each exemplar. The regression analysis technique was chosen to examine the correlation between antibiotic consumption expressed in DDD/1000 bed days and time. Regression analysis was used to describe the distribution of a dependent variable. The main aim of the analysis is to search for independent variables that help in explaining the variation of the dependent variable. Data on any outbreaks of microorganisms were obtained from the microbiology department and the antimicrobial pharmacist. The level of significance of mean difference is displayed as the number of asterisks as follows:

- one asterisk (*) represents significant level where $p \leq 0.05$
- two asterisks (**) represent very significant level where $p \leq 0.01$
- Three asterisks (***) represent highly significant level where $p \leq 0.001$
- NS represents not significant level where $p > 0.05$

6.1 Amoxicillin

Amoxicillin is the primary recommended treatment in national guidelines for the majority of upper and lower respiratory tract infections (Public Health England, 2014). Amoxicillin was UHBFT formulary during both the periods with and without structured prescribing. The consumption of amoxicillin decreased from 117.5 to 105.5 DDD per 1000 bed days between 2012/3 and 2015/6 as shown in Figure 64. There was no correlation between amoxicillin consumption and time in the period with structured prescribing ($R^2=0.0072$) and in the period without structured prescribing ($R^2=0.005$) as shown in figure 65. The mean for amoxicillin use in the period with structured prescribing was 111 ± 7 DDD/1000 bed days. The mean for amoxicillin use in the period without structured

prescribing was 107 ± 4.1 DDD/1000 bed days. The difference between the two means was + 4.29 DDD/1000 bed days for amoxicillin use in the periods with and without structured prescribing but this difference was not statistically significant, ($p= 0.597$).

Figure 64: Consumption of amoxicillin, expressed as DDD per 1000 bed days, 2012-2016

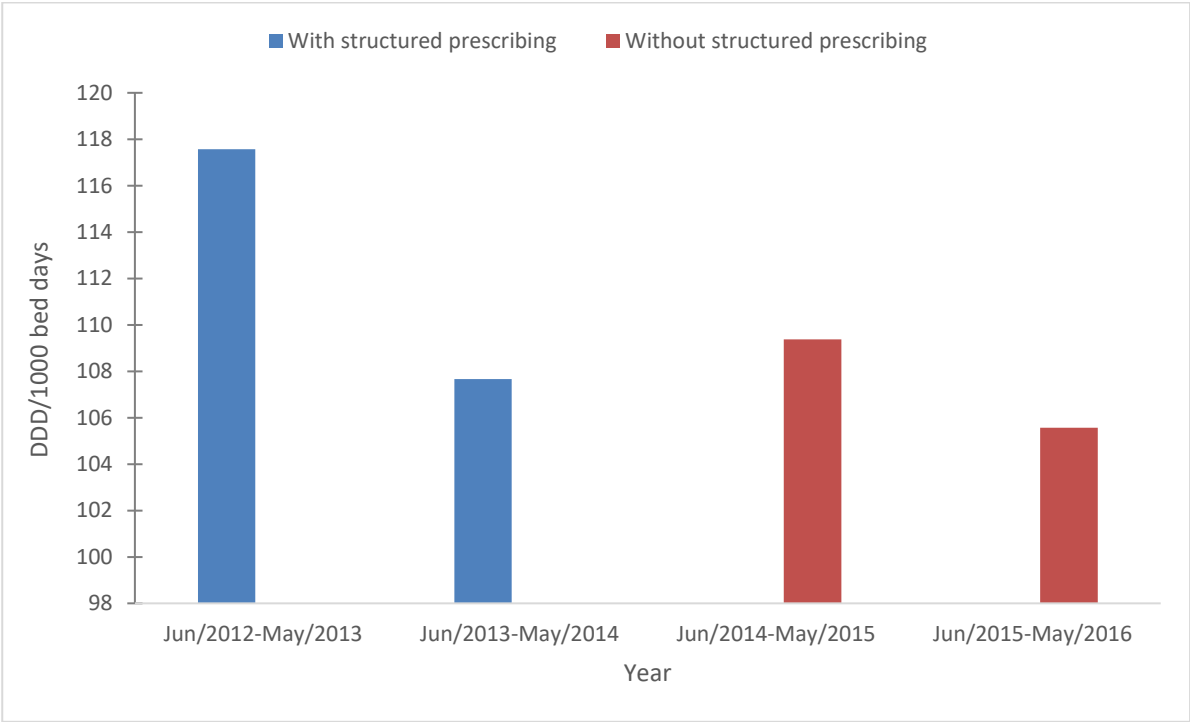
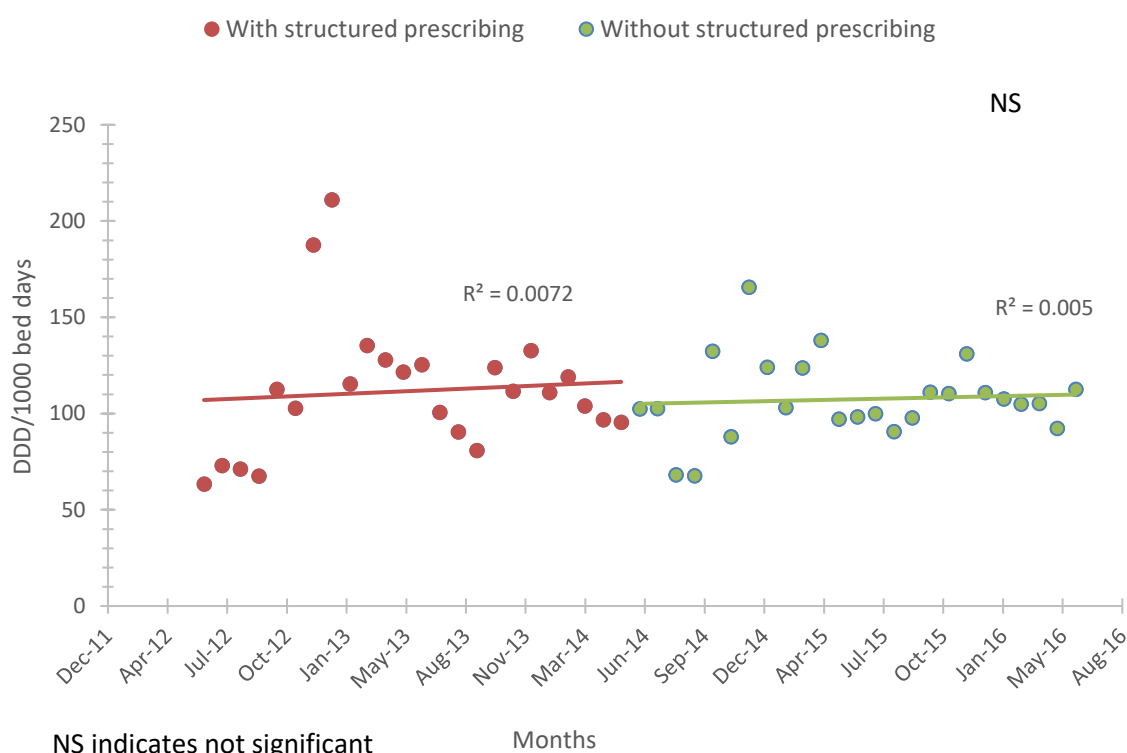


Figure 65: Monthly consumption of amoxicillin reported as DDD/1000 bed days. Trend lines established by linear regression before and after deployment of structured prescribing are shown



6.2 Co-amoxiclav

Co-amoxiclav is a combination of a broad-spectrum antibiotic and clavulanic acid and is active against a wide range of Gram-positive and Gram-negative pathogens. The national community infection guidelines include co-amoxiclav as an option for the treatment of urinary tract infections (Public Health England, 2014). Co-amoxiclav was UHBFT formulary during both the periods with and without structured prescribing. The consumption of co-amoxiclav increased from 300 to 344.5 DDD per 1000 bed days between 2012/3 and 2015/6 as shown in Figure 66. There was no correlation between co-amoxiclav consumption and time in the period with structured prescribing ($R^2=0.0108$) and a weak positive correlation between co-amoxiclav consumption and time in the period without structured prescribing ($R^2=0.1492$) (see Figure 67). The mean for co-amoxiclav use in the period with structured prescribing was 301.7 ± 11.6 DDD/1000 bed days. The mean for co-amoxiclav use in the period without structured prescribing was 333.3 ± 8.4 DDD/1000 bed days. The difference between

the two means was -31.6 DDD/1000 bed days for co-amoxiclav use in the periods with and without structured prescribing and this difference was statistically significant, ($p=0.031$). The use of structured prescribing was associated with a decrease in the use of amoxicillin as co-amoxiclav is replacing amoxicillin use. The use of co-amoxiclav was increased due to policy for treating low-risk patients with febrile neutropenia.

Figure 66: Consumption of co-amoxiclav, expressed as DDD per 1000 bed days, 2012-2016

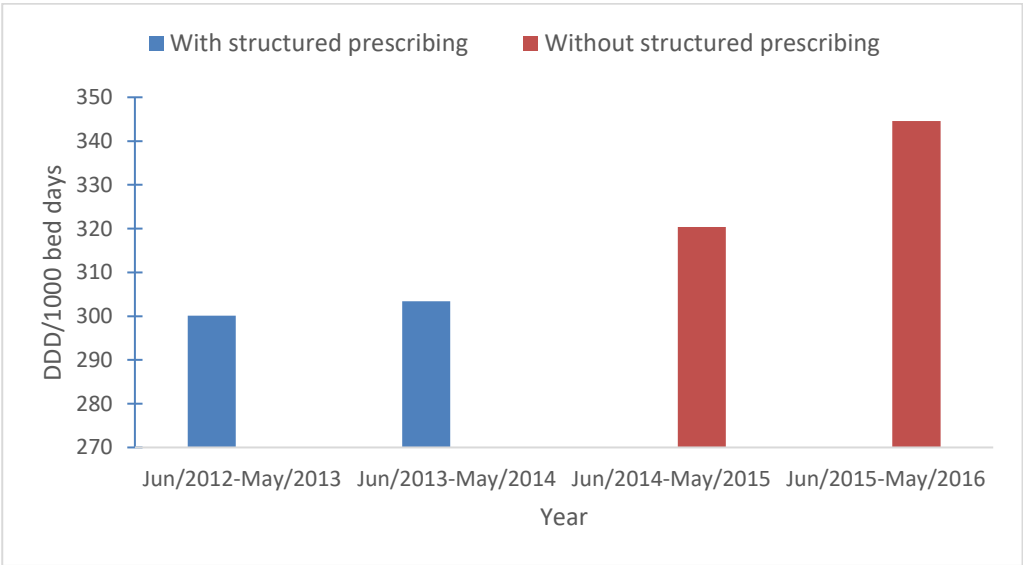
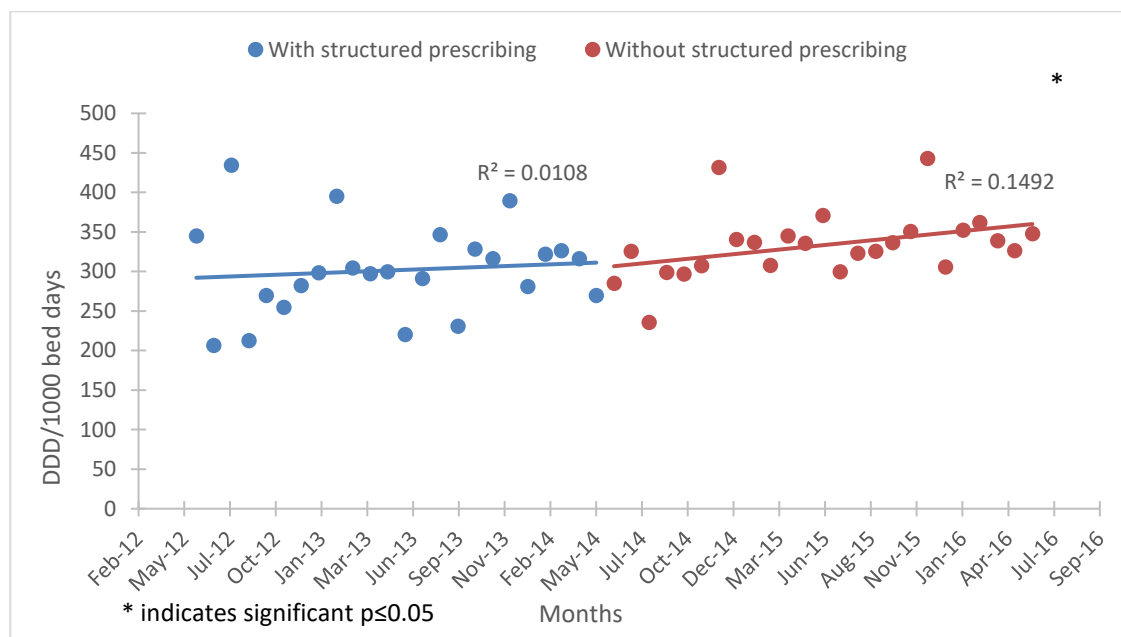


Figure 67: Monthly consumption of co-amoxiclav reported as DDD/1000 bed days. Trend lines established by linear regression before and after deployment of structured prescribing are shown



6.3 Ceftriaxone

Ceftriaxone is a third-generation cephalosporin active against Gram-positive pathogens such as streptococci and staphylococci. Ceftriaxone is indicated for treatment of both community and hospital acquired pneumonia. However, national guidelines do not recommend its use empirically, except for the treatment of meningitis and gonorrhoea, because indiscriminate use can predispose patients to *Clostridium difficile* infections (Public Health England, 2014). UHBFT is a specialist centre for neurology and will have an above average caseload of meningitis. Ceftriaxone use increased but other cephalosporins decreased. Ceftriaxone was UHBFT formulary during both the periods with and without structured prescribing. The consumption of ceftriaxone increased from 5.8 to 14.1 DDD per 1000 bed days between 2012/3 and 2015/6. Figure 68 shows the annual consumption of ceftriaxone. Ceftriaxone use increased but other cephalosporins decreased. There was a weak positive correlation between ceftriaxone consumption and time in the period with structured prescribing ($R^2=0.2371$) and no correlation between ceftriaxone consumption and time in the period without structured prescribing ($R^2=0.029$) (see Figure 69). The mean for ceftriaxone use in the period with structured prescribing

was 7.4 ± 0.6 DDD/1000 bed days. The mean for ceftriaxone use in the period without structured prescribing was 13.3 ± 0.78 DDD/1000 bed days. The difference between the two means was -5.88 DDD/1000 bed days for ceftriaxone use in the periods with and without structured prescribing and this difference was statistically significant, ($p < 0.01$).

Figure 68: Consumption of ceftriaxone, expressed as DDD per 1000 bed days, 2012-2016

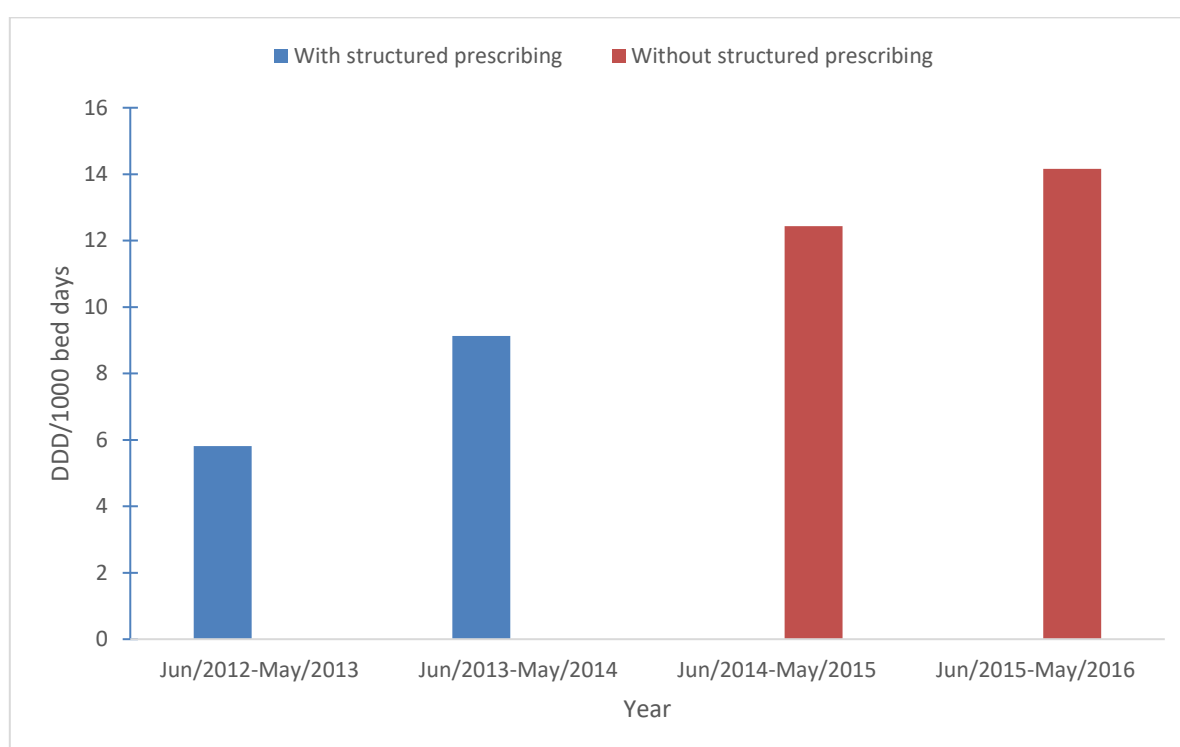
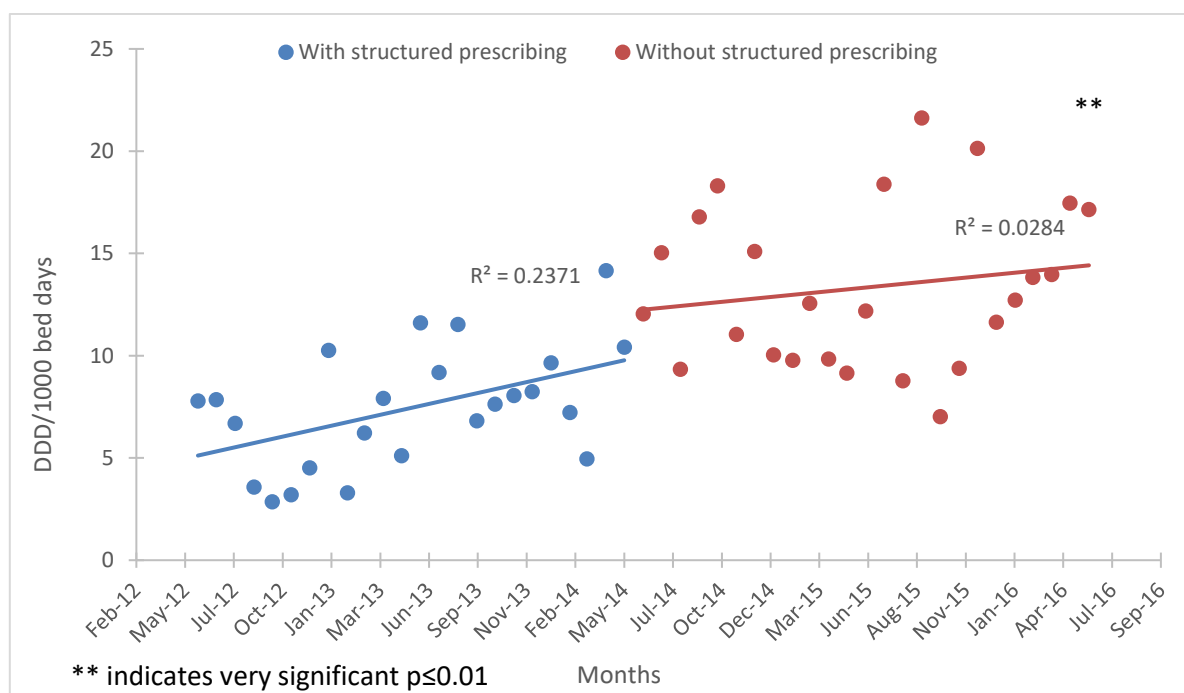


Figure 69: Monthly consumption of ceftriaxone reported as DDD/1000 bed days. Trend lines established by linear regression before and after deployment of structured prescribing are shown



6.4 Meropenem

Meropenem is a carbapenem antibiotic used exclusively within hospitals for the treatment of infections caused by multidrug resistant pathogens including pneumonias, meningitis and fever in patients with neutropenia (Public Health England, 2014). Meropenem may be used in patients with renal failure. Meropenem was UHBFT formulary during both the periods with and without structured prescribing. The consumption of meropenem increased from 98.9 to 112.2 DDD per 1000 bed days between 2012/3 and 2015/6. Figure 70 shows the annual consumption of meropenem. There was no correlation between meropenem consumption and time in the period with structured prescribing ($R^2=0.0209$) and in the period without structured prescribing ($R^2=0.0226$) (See Figure 71). The mean for meropenem use in the period with structured prescribing was 96.53 ± 1.94 DDD/1000 bed days. The mean for meropenem use in the period without structured prescribing was 110.7 ± 2.75 DDD/1000 bed days. The difference between the two means was -14.52 DDD/1000 bed days for meropenem use

in the periods with and without structured prescribing and this difference was statistically significant, (p<0.01).

Figure 70: Consumption of meropenem, expressed as DDD per 1000 bed days, 2012-2016

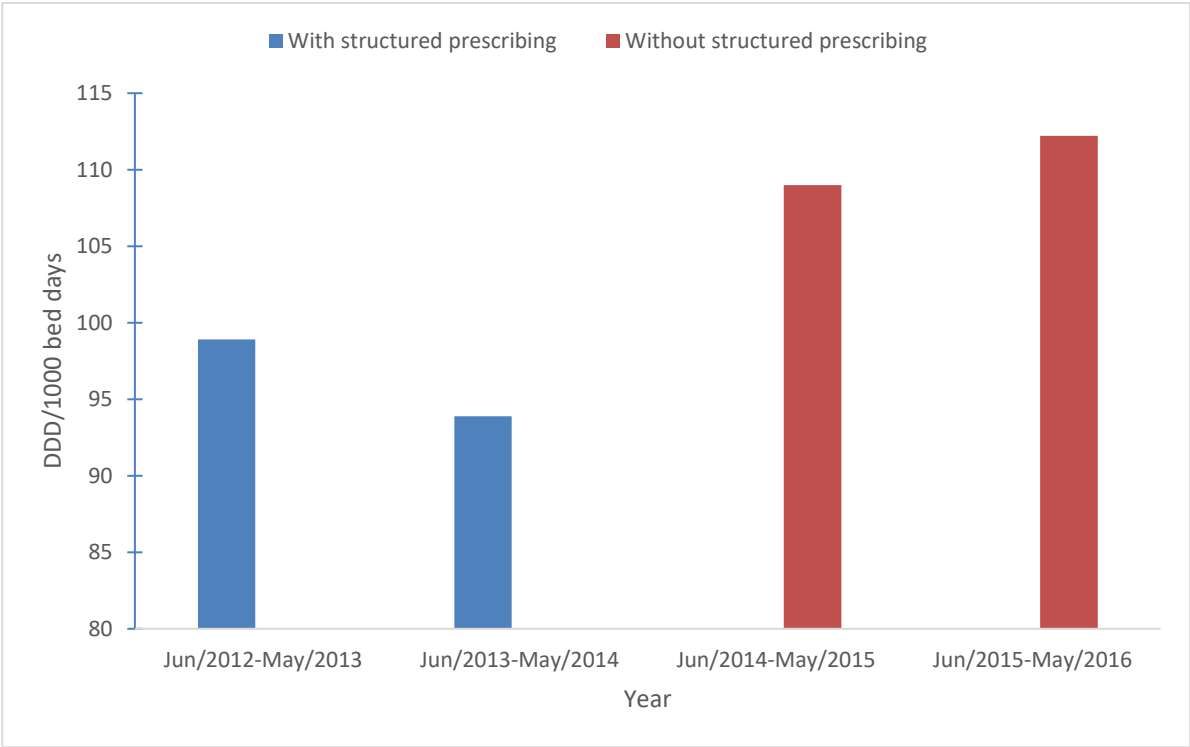
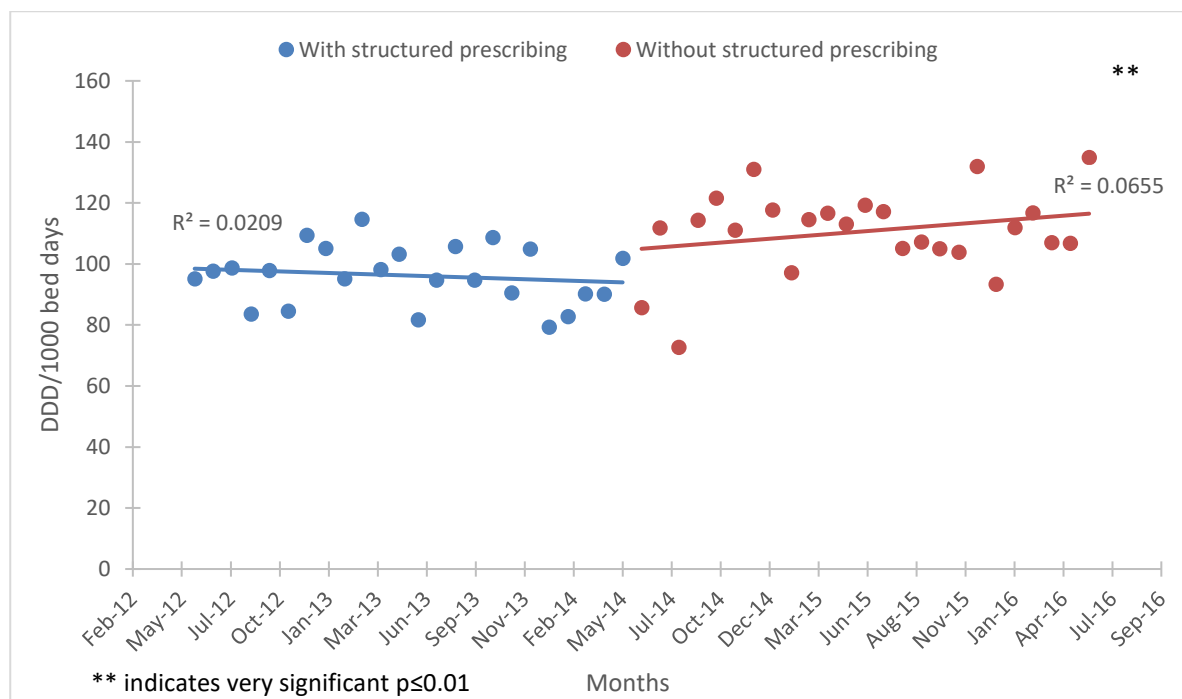


Figure 71: Monthly consumption of meropenem reported as DDD/1000 bed days. Trend lines established by linear regression before and after deployment of structured prescribing are shown



6.5 Gentamicin

Gentamicin is used as part of the therapeutic regimen for the treatment of sepsis and urinary tract infections within English hospitals and is particularly active against Gram-negative organisms which are resistant to other agents (Public Health England, 2014). Gentamicin was UHBFT formulary during both the periods with and without structured prescribing. The consumption of gentamicin decreased from 17.2 to 15.2 DDD per 1000 bed days between 2012/3 and 2015/6. Figure 72 shows the annual consumption of gentamicin. There was a weak positive correlation between gentamicin consumption and time in the period with structured prescribing ($R^2=0.1784$) and no correlation between gentamicin consumption and time in the period without structured prescribing ($R^2=0.0315$) (See Figure 73). The mean for gentamicin use in the period with structured prescribing was 18.14 ± 0.68 DDD/1000 bed days. The mean for gentamicin use in the period without structured prescribing

was 15.6 ± 0.488 DDD/1000 bed days. The difference between the two means was +2.51 DDD/1000 bed days for gentamicin use in the periods with and without structured prescribing and this difference was statistically significant, ($p=0.004$).

Figure 72: Consumption of gentamicin, expressed as DDD per 1000 bed days, 2012-2016

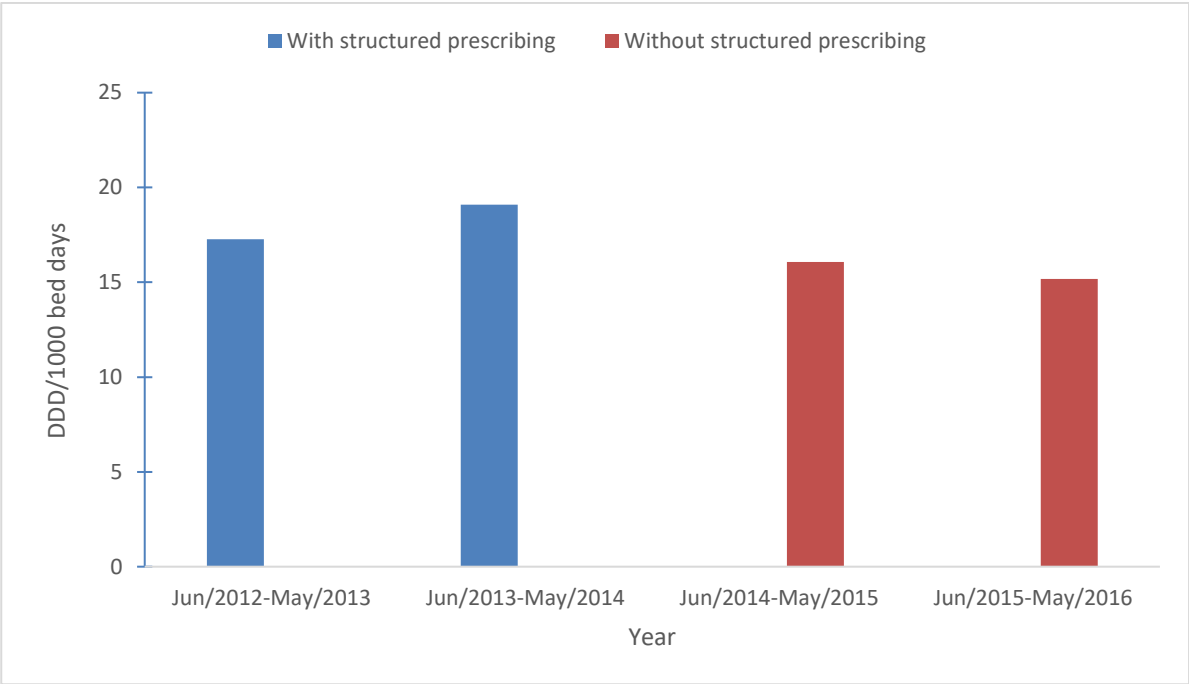
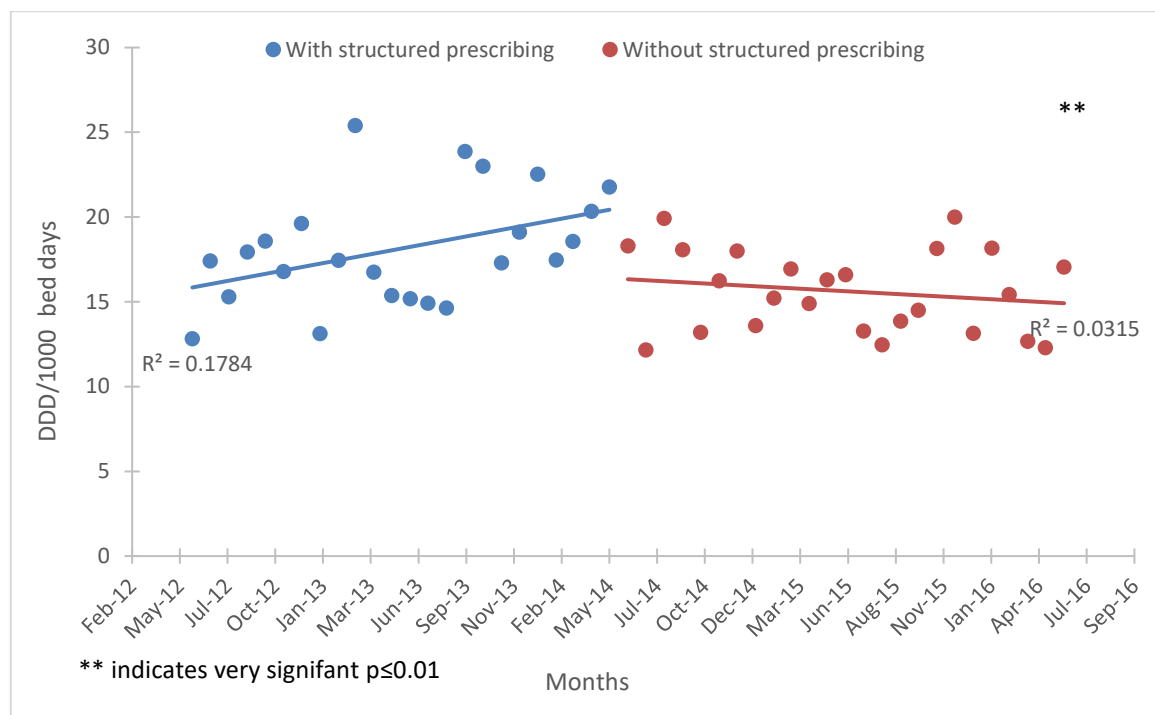


Figure 73: Monthly consumption of gentamicin reported as DDD/1000 bed days. Trend lines established by linear regression before and after deployment of structured prescribing are shown



6.6 Clarithromycin

Clarithromycin is used for the treatment of most Gram-positive and respiratory Gram-negative pathogens. National infection guidelines include clarithromycin as an alternative agent for treating upper and lower respiratory tract infections in patients allergic to penicillins (Public Health England, 2014). It is also indicated for the eradication of *H. pylori* in patients with duodenal ulcers. Clarithromycin was UHBFT formulary during both the periods with and without structured prescribing. The consumption of clarithromycin increased from 83 to 110 DDD per 1000 bed days between 2012/3 and 2015/6. Figure 74 shows the annual consumption of clarithromycin. There was a moderate positive correlation between clarithromycin consumption and time in the period with structured prescribing ($R^2=0.5423$) and no correlation between clarithromycin consumption and time in the period without structured prescribing ($R^2=0.0041$) (See Figure 75). The mean for clarithromycin use in the period with structured prescribing was 102.6 ± 9.9 DDD/1000 bed days. The mean for clarithromycin use in the period without structured prescribing was 110 ± 3.6

DDD/1000 bed days. The difference between the two means was -7.88 DDD/1000 bed days for clarithromycin use in the periods with and without structured prescribing but this difference was not statistically significant, (p=0.490).

Figure 74: Consumption of clarithromycin, expressed as DDD per 1000 bed days, 2012-2016

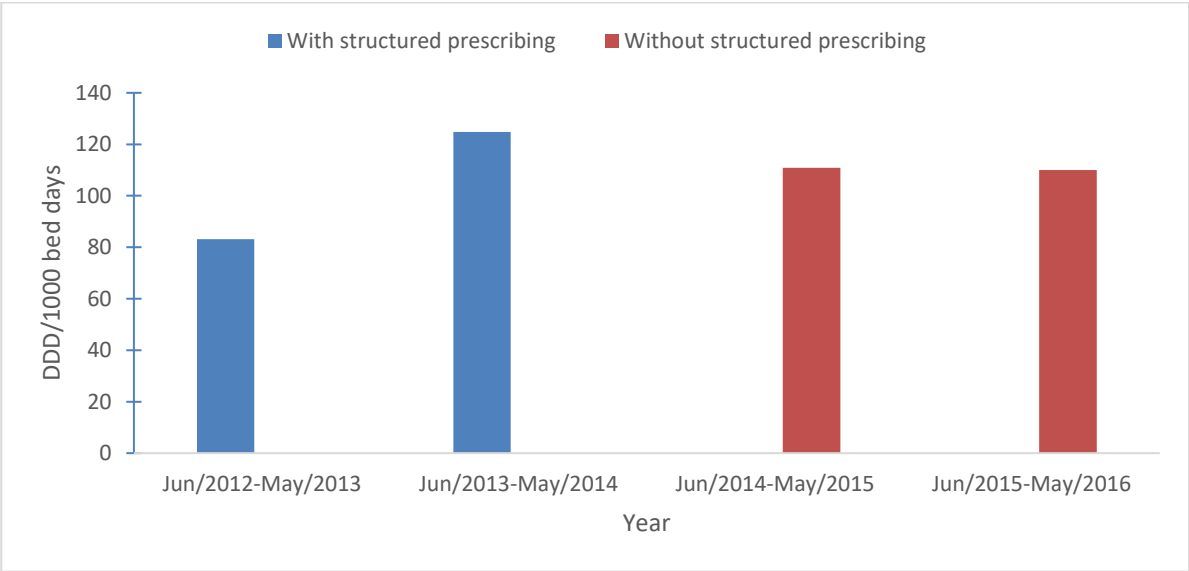
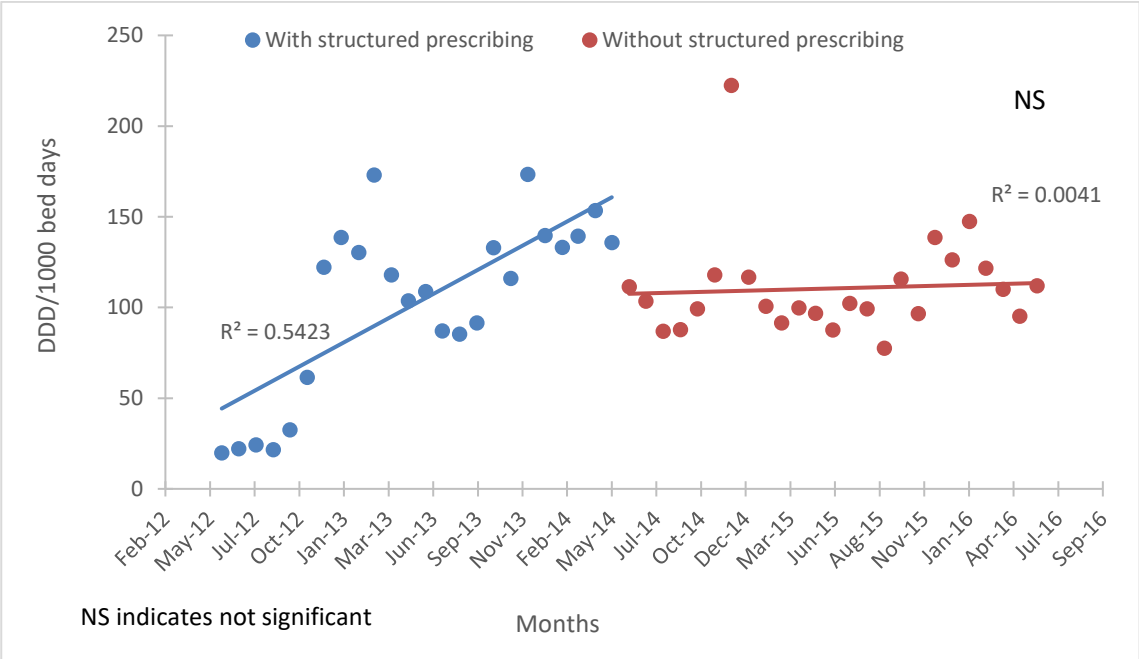


Figure 75: Monthly consumption of clarithromycin reported as DDD/1000 bed days. Trend lines established by linear regression before and after deployment of structured prescribing are shown



6.7 Ciprofloxacin

Ciprofloxacin is a broad-spectrum antibiotic used at UHBFT for the treatment of bacterial infections such as bone infections, respiratory tract infections, urinary tract infections and intraabdominal infections (Public Health England, 2014). The use of ciprofloxacin is implicated as a cause of increase in *clostridium difficile* cases. Ciprofloxacin was UHBFT formulary during both the periods with and without structured prescribing. The consumption of ciprofloxacin decreased from 75 to 69 DDD per 1000 bed days between 2012/3 and 2015/6. The use of ciprofloxacin increased from 75 to 116 DDD per 1000 bed days between 2012/3 and 2013/4. Figure 76 shows the annual consumption of ciprofloxacin. There was a strong positive correlation between ciprofloxacin consumption and time in the period with structured prescribing ($R^2=0.66$) and a moderate negative correlation between ciprofloxacin consumption and time in the period without structured prescribing ($R^2=0.5417$) (See Figure 77). The mean for ciprofloxacin use in the period with structured prescribing was 94.64 ± 7.77 DDD/1000 bed days. The mean for ciprofloxacin use in the period without structured prescribing was 81 ± 4.16 DDD/1000 bed days. The difference between the two means was +13.6 DDD/1000 bed days for ciprofloxacin use in the periods with and without structured prescribing but this difference was not statistically significant, ($p=0.125$).

Figure 76: Consumption of ciprofloxacin, expressed as DDD per 1000 bed days, 2012-2016

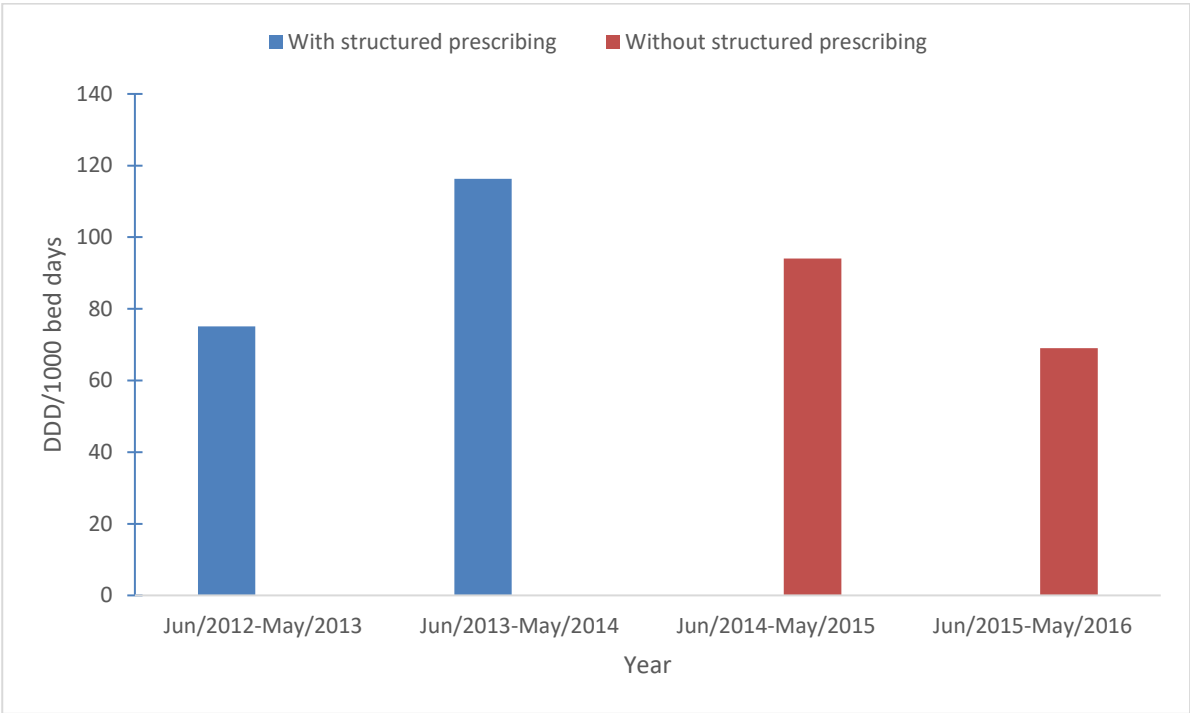
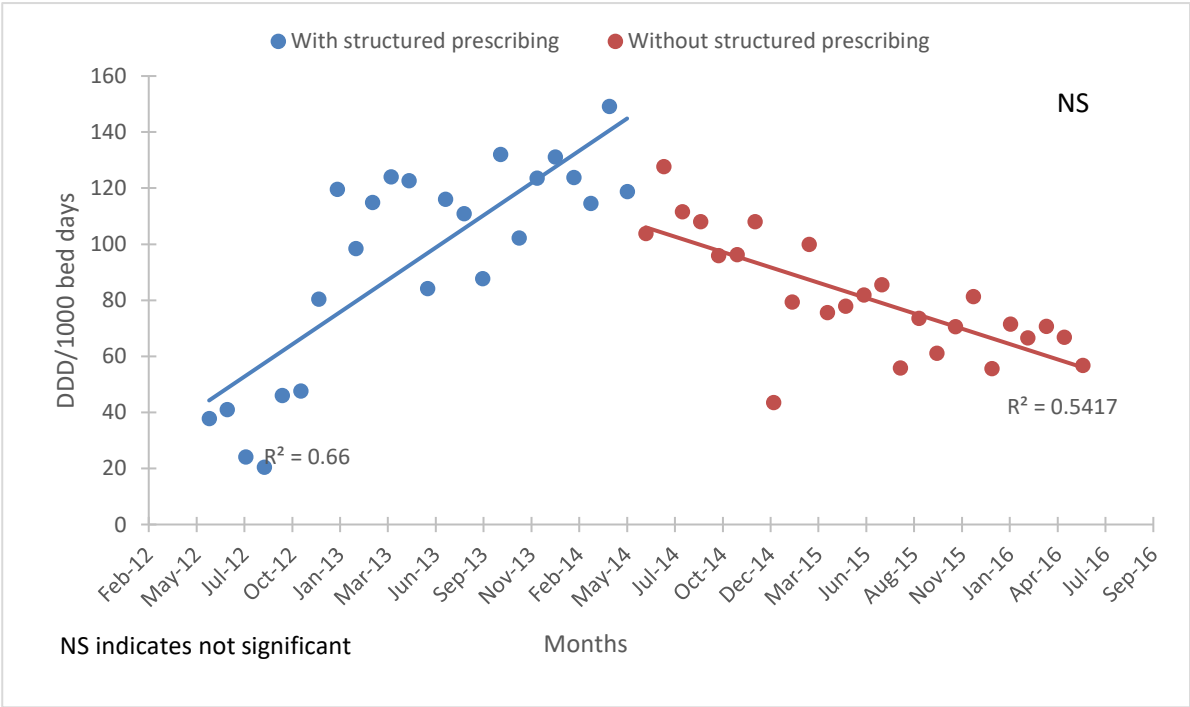


Figure 77: Monthly consumption of ciprofloxacin reported as DDD/1000 bed days. Trend lines established by linear regression before and after deployment of structured prescribing are shown



6.8 Levofloxacin

Levofloxacin is a broad-spectrum antibiotic active against Gram-positive and Gram-negative pathogens and is used to treat urinary tract infections and hospital-acquired pneumonia (Public Health England, 2014). It is an alternative quinolone to ciprofloxacin. Levofloxacin was non UHBFT formulary during the period with structured prescribing and was UHBFT formulary during the period without structured prescribing. The consumption of levofloxacin increased from 18 to 28.7 DDD per 1000 bed days between 2012/3 and 2015/6. The consumption of levofloxacin decreased from 18 to 12.8 DDD per 1000 bed days between 2012/3 and 2013/4. Figure 78 shows the annual consumption of levofloxacin. There was no correlation between levofloxacin consumption and time in the period with structured prescribing ($R^2=0.0403$) and a weak positive correlation between levofloxacin and time in the period without structured prescribing ($R^2=0.357$) (See Figure 79). The mean for levofloxacin use in the period with structured prescribing was 15.4 ± 1.29 DDD/1000 bed days. The mean for levofloxacin use in the period without structured prescribing was 24.3 ± 2.04 DDD/1000 bed days. The difference between the two means was -8.9 DDD/1000 bed days for levofloxacin use in the periods with and without structured prescribing and this difference was statistically significant, ($p=0.001$).

Figure 78: Consumption of levofloxacin, expressed as DDD per 1000 bed days, 2012-2016

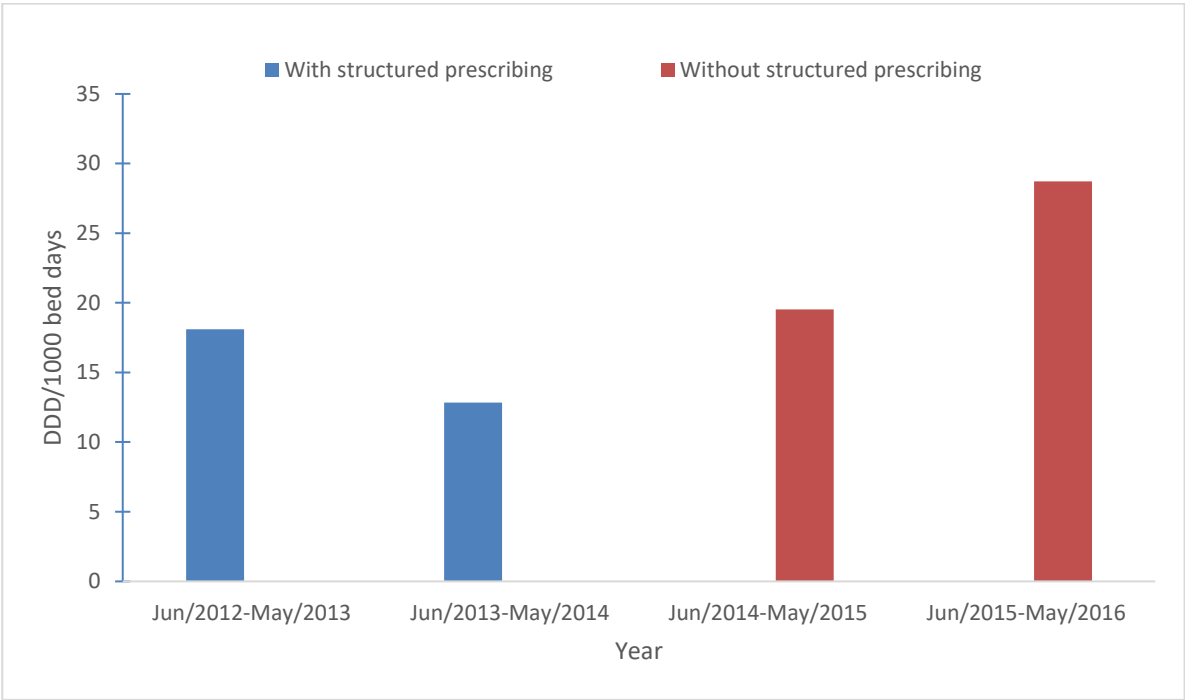
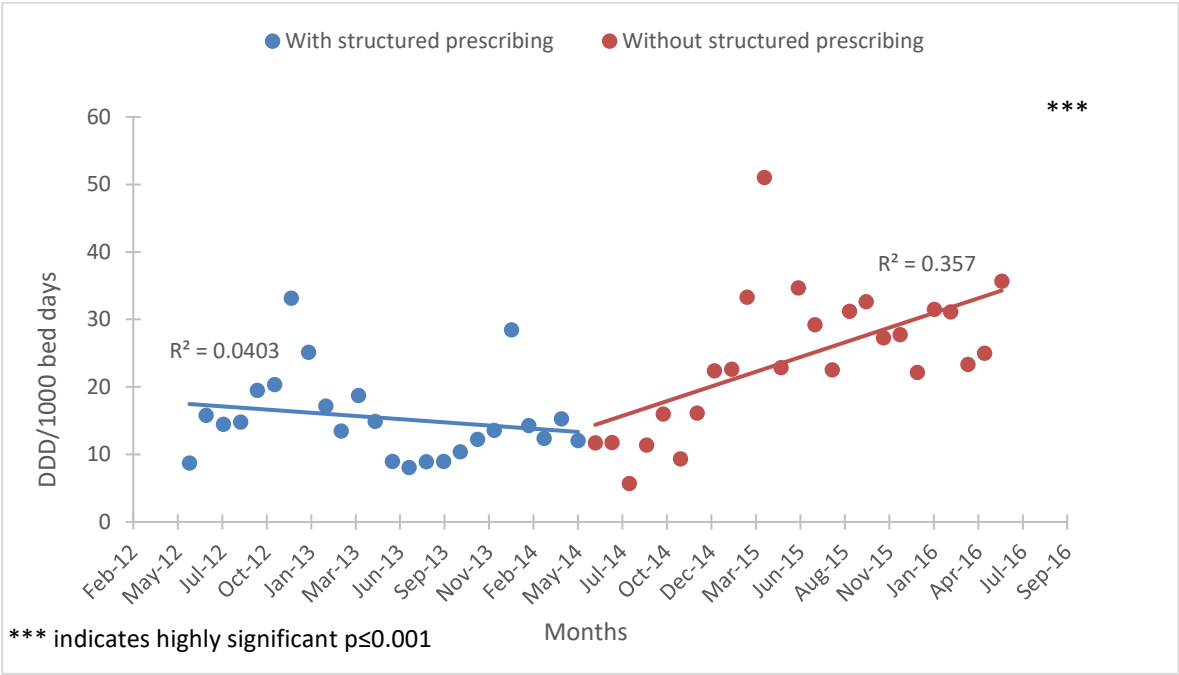


Figure 79 : Monthly consumption of levofloxacin reported as DDD/1000 bed days. Trend lines established by linear regression before and after deployment of structured prescribing are shown.



6.9 Doxycycline

Doxycycline is an antibiotic used extensively at UHBFT for the treatment of Gram-positive infections. National infection guidance in primary care includes doxycycline as an alternative agent to amoxicillin for the treatment of upper and lower respiratory tract infections (Public Health England, 2014). Doxycycline was UHBFT formulary during both the periods with and without structured prescribing. The consumption of doxycycline decreased from 77.2 to 58.2 DDD per 1000 bed days between 2012/3 and 2015/6. Figure 80 shows the annual consumption of doxycycline. There was a weak positive correlation between doxycycline consumption and time in the period with structured prescribing ($R^2=0.114$) and no correlation between doxycycline consumption and time in the period without structured prescribing ($R^2=0.0465$) (See Figure 81). The mean for doxycycline use in the period with structured prescribing was 78.5 ± 5.3 DDD/1000 bed days. The mean for doxycycline use in the period without structured prescribing was 61.6 ± 3.3 DDD/1000 bed days. The difference between the two means was $+16.84$ DDD/1000 bed days for doxycycline use in the periods with and without structured prescribing and this difference was statistically significant, ($p=0.009$).

Figure 80: Consumption of doxycycline, expressed as DDD per 1000 bed days, 2012-2016

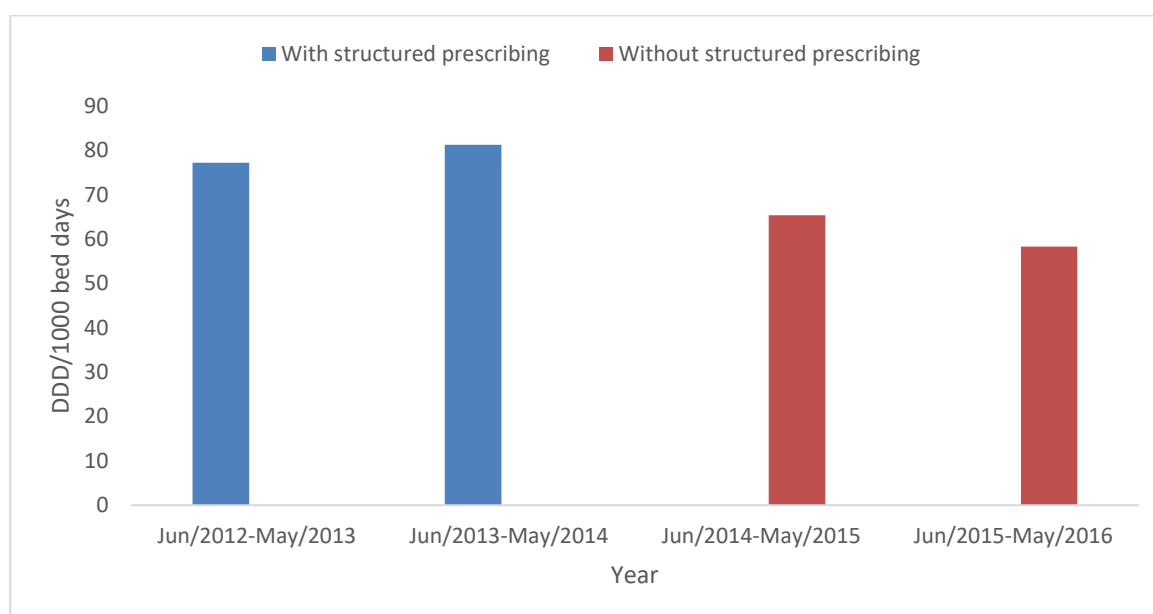
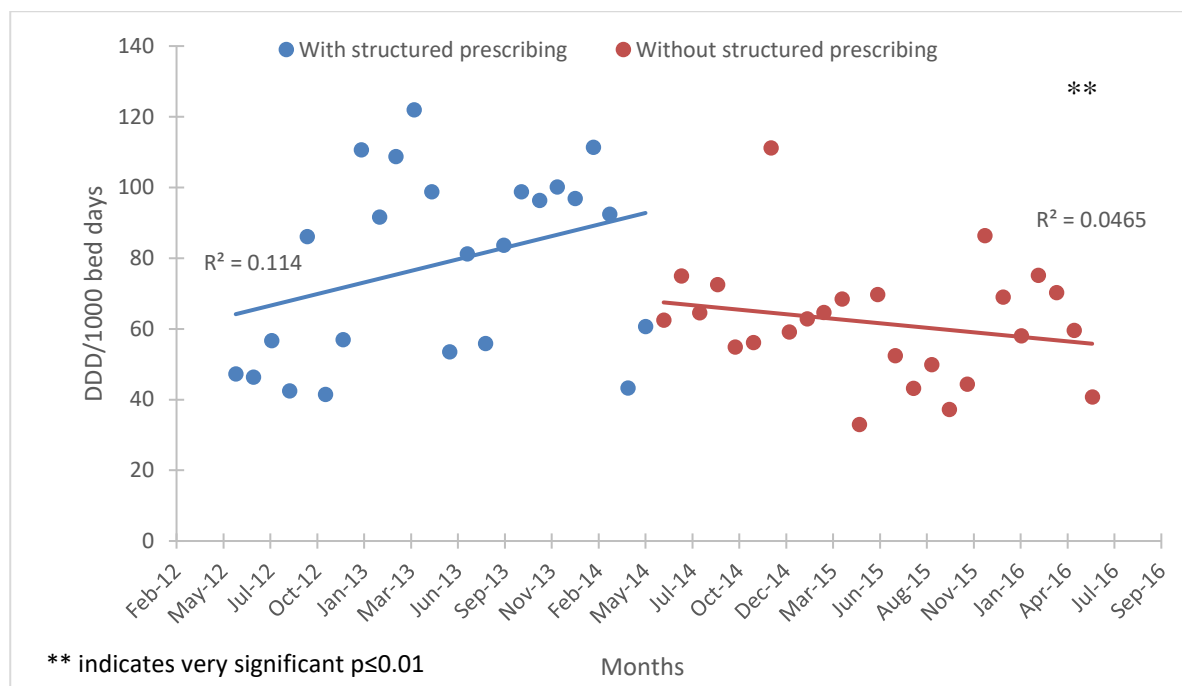


Figure 81: Monthly consumption of doxycycline reported as DDD/1000 bed days. Trend lines established by linear regression before and after deployment of structured prescribing are shown.



6.10 Rifampicin

Rifampicin is an oral antimycobacterial agent used at UHBFT to treat bacterial infections such as tuberculosis, leprosy and Legionnaires' disease. Rifampicin is also used for meningococcal infections. According to NICE guideline, rifampicin is used for the treatment of tuberculosis (Public Health England, 2014). The use of rifampicin would be expected to reflect the number of tuberculosis cases seen and use of decision support ensure adherence to guidelines. Rifampicin was UHBFT formulary during both the periods with and without structured prescribing. The consumption of rifampicin increased from 45.5 to 47.1 DDD per 1000 bed days between 2012/3 and 2015/6. The use of rifampicin decreased from 45.5 to 39.9 DDD per 1000 bed days between 2012/3 and 2014/5. Figure 82 shows the annual consumption of rifampicin. There was no correlation between rifampicin consumption and time in the period with structured prescribing ($R^2=0.0139$) and a weak positive correlation between rifampicin consumption and time in the period without structured prescribing ($R^2=0.1467$) (See Figure 83). The mean for rifampicin use in the period with structured prescribing

was 45.3 ± 1.98 DDD/1000 bed days. The mean for rifampicin use in the period without structured prescribing was 43.35 ± 2.2 DDD/1000 bed days. The difference between the two means was +1.94 DDD/1000 bed days for rifampicin use in the periods with and without structured prescribing but this difference was not statistically significant, ($p=0.516$).

Figure 82: Consumption of rifampicin, expressed as DDD per 1000 bed days, 2012-2016

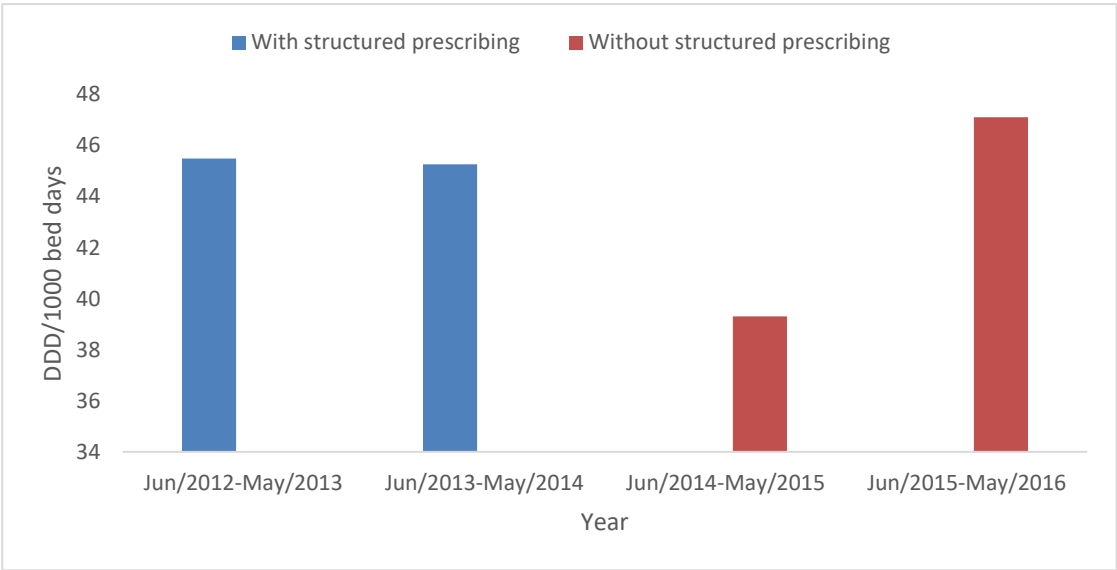
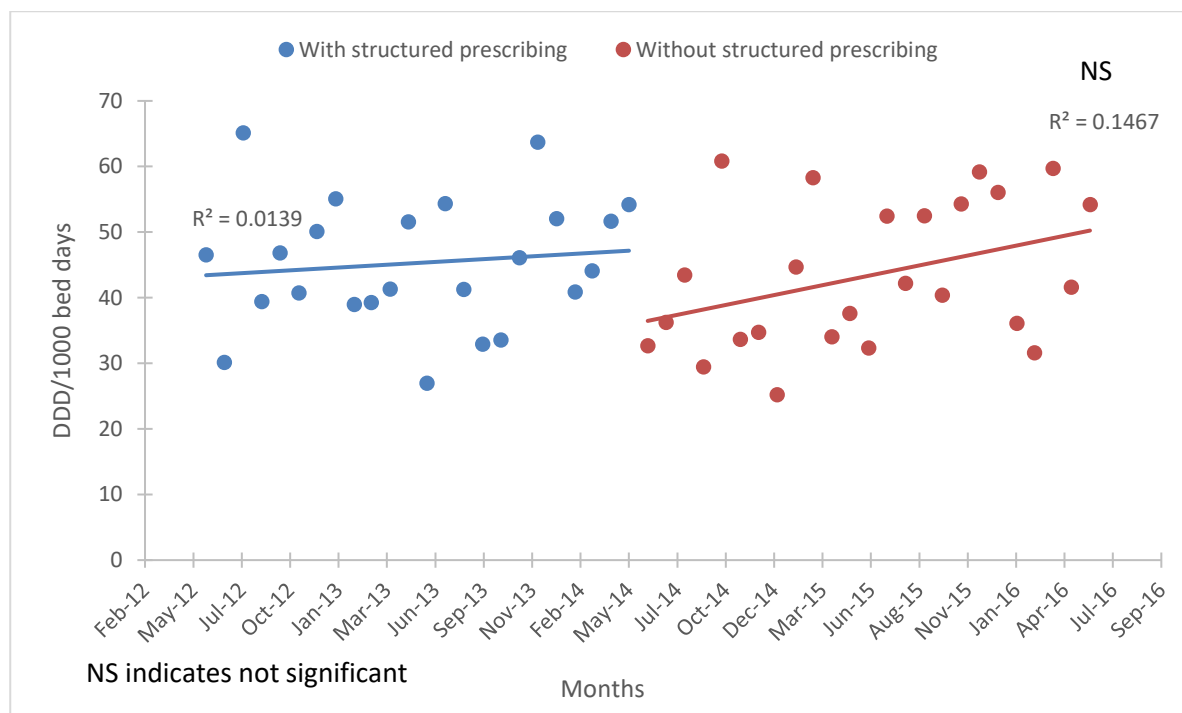


Figure 83: Monthly consumption of rifampicin reported as DDD/1000 bed days. Trend lines established by linear regression before and after deployment of structured prescribing are shown



6.11 Vancomycin

Vancomycin is a glycopeptide, which may be administered intravenously to treat infections due to resistant Gram-positive pathogens such as methicillin resistant *Staphylococcus aureus* (MRSA) and enterococci (Public Health England, 2014). It was chosen as an exemplar because vancomycin resistant enterococci (VRE) have emerged since the 1980's and become a problem in hospitals across the World and VRE is a cause of hospital acquired infection which can be difficult to treat. Vancomycin must be given intravenously for treating systemic infections since it is not absorbed in the intestine. It is a large hydrophilic molecule that partition poorly across the gastrointestinal mucosa. The only approved indication for oral vancomycin is in the treatment of pseudomembranous colitis where it must be given orally to reach the site of infection in the colon. Vancomycin was UHBFT formulary during both the periods with and without structured prescribing. The consumption of vancomycin increased from 14.2 to 31.5 DDD per 1000 bed days between 2012/3 and 2015/6. Figure

84 shows the annual consumption of vancomycin. There was a moderate positive correlation between vancomycin consumption and time in the period with structured prescribing ($R^2=0.5464$) and no correlation between vancomycin consumption and time in the period without structured prescribing ($R^2=0.0004$) (See Figure 85). The mean for vancomycin use in the period with structured prescribing was 19.5 ± 2 DDD/1000 bed days. The mean for vancomycin use in the period without structured prescribing was 31.2 ± 0.8 DDD/1000 bed days. The difference between the two means was -11.7 DDD/1000 bed days for vancomycin use in the periods with and without structured prescribing and this difference was statistically significant, ($p<0.01$). The use of oral and intravenous vancomycin increased over the four-year period shown in Figure 84b.

Figure 84: Consumption of vancomycin, expressed as DDD per 1000 bed days, 2012-2016

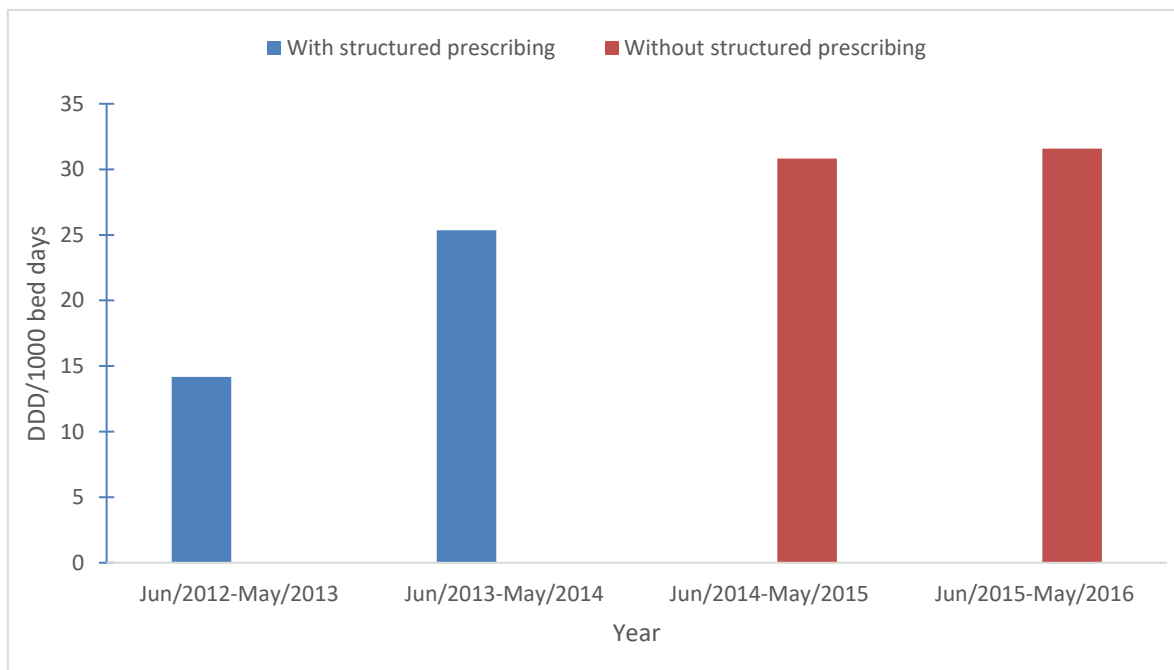
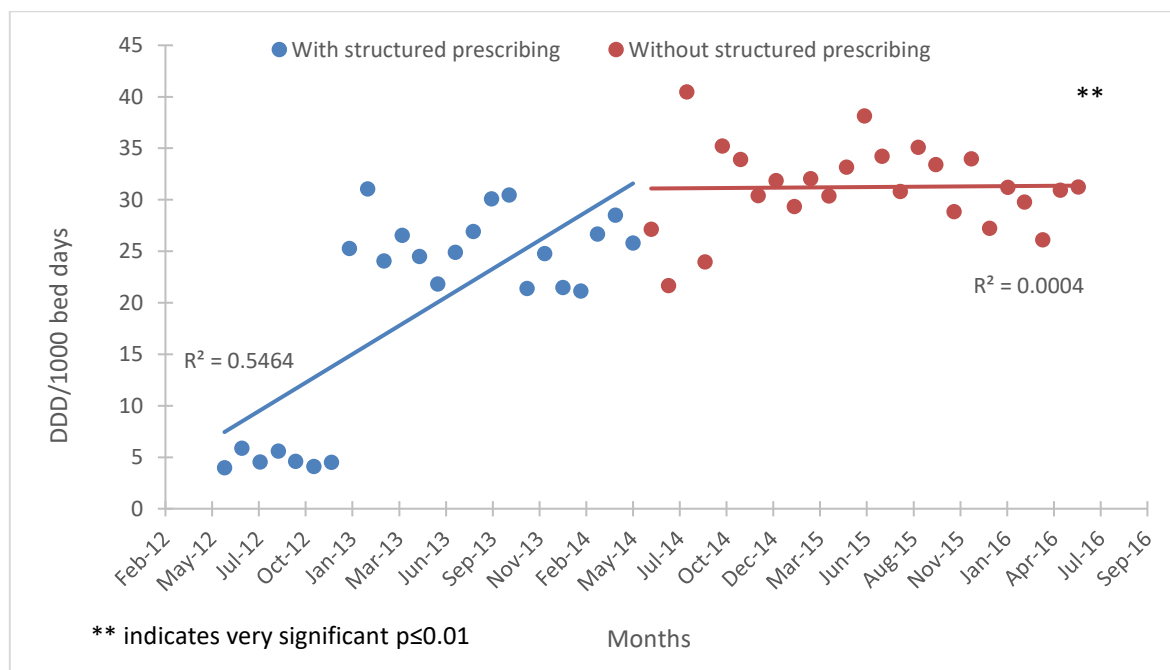


Figure 85: Monthly consumption of vancomycin reported as DDD/1000 bed days. Trend lines established by linear regression before and after deployment of structured prescribing are shown



6.12 Metronidazole

Metronidazole is an antibiotic and an antiprotozoal used extensively at UHBFT for the treatment of pelvic inflammatory disease, endocarditis and bacterial vaginosis (Public Health England, 2014). It is widely used to treat anaerobic infections and used in *H pylori* eradication and for the treatment of *C.diff* infections (Public Health England, 2014). Metronidazole was UHBFT formulary during both the periods with and without structured prescribing. The consumption of metronidazole decreased from 58.3 to 44.1 DDD per 1000 bed days between 2012/3 and 2015/6. Figure 86 shows the annual consumption of metronidazole. There was a weak negative correlation between metronidazole consumption and time in the period with structured prescribing ($R^2=0.309$) and no correlation between metronidazole consumption and time in the period without structured prescribing ($R^2=0.0018$) (See Figure 87). The mean for metronidazole use in the period with structured

prescribing was 54.6 ± 1.98 DDD/1000 bed days. The mean for metronidazole use in the period without structured prescribing was 45.6 ± 1.8 DDD/1000 bed days. The difference between the two means was + 8.96 DDD/1000 bed days for metronidazole use in the periods with and without structured prescribing and this difference was statistically significant, ($p=0.002$).

Figure 86: Consumption of metronidazole, expressed as DDD per 1000 bed days, 2012-2016

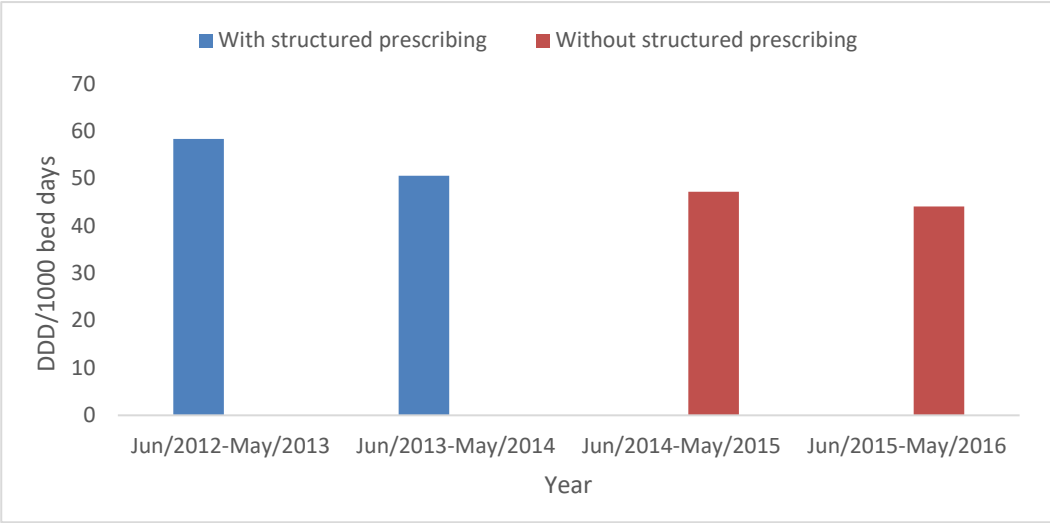
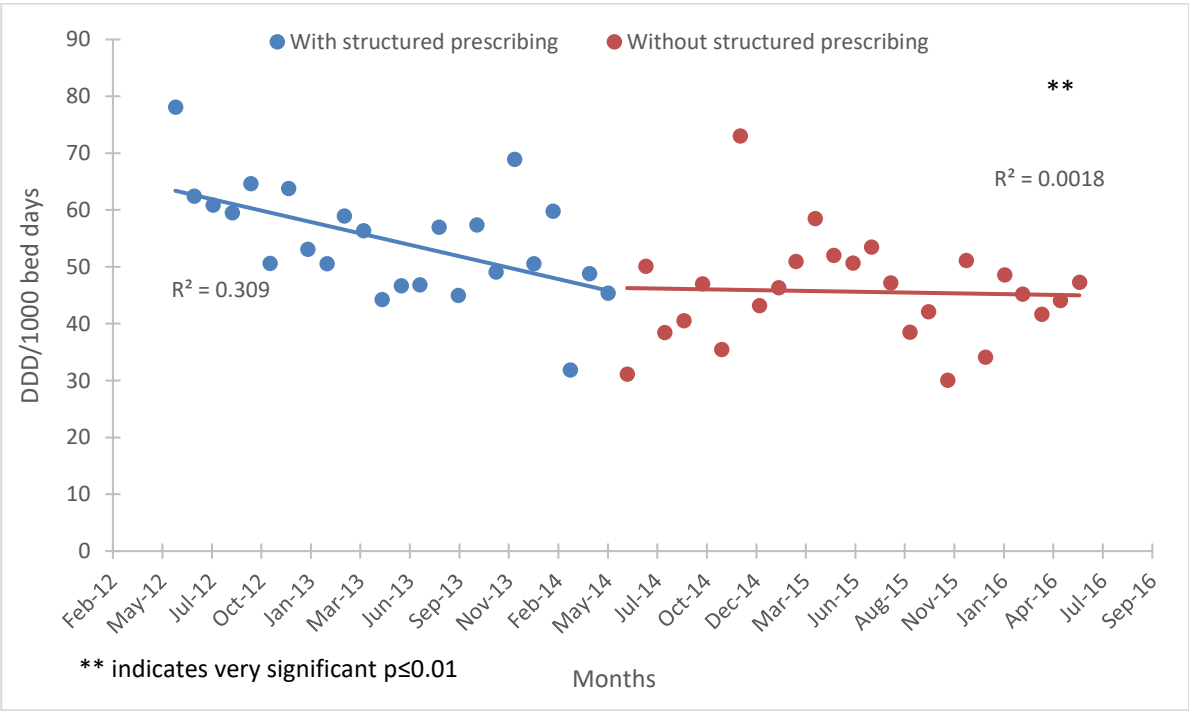


Figure 87: Monthly consumption of metronidazole reported as DDD/1000 bed days. Trend lines established by linear regression before and after deployment of structured prescribing are shown



6.13 Clindamycin

Clindamycin is an antibiotic used for the treatment of bacterial infections such as bone infections, otitis media, endocarditis and pneumonia (Public Health England, 2014). Clindamycin is used to treat anaerobic infections caused by susceptible anaerobic bacteria and infections of skin and respiratory tract (Public Health England, 2014). Clindamycin was UHBFT formulary during both the periods with and without structured prescribing. The consumption of clindamycin decreased from 29.4 to 24.1 DDD per 1000 bed days between 2012/3 and 2015/6. Figure 88 shows the annual consumption of clindamycin. There was a weak negative correlation between antibiotic consumption and time for in the period with structured prescribing ($R^2=0.211$) and a weak negative correlation between clindamycin consumption and time in the period without structured prescribing ($R^2= 0.1542$) (See Figure 89). The mean for clindamycin use in the period with structured prescribing was 28 ± 1.06 DDD/1000 bed days. The mean for clindamycin use in the period without structured prescribing was 26.7 ± 1.3 DDD/1000 bed days. The difference between the two means was $+ 1.29$ DDD/1000 bed days for clindamycin use in the periods with and without structured prescribing but this difference was not statistically significant, ($p=0.455$).

Figure 88: Consumption of clindamycin, expressed as DDD per 1000 bed days, 2012-2016

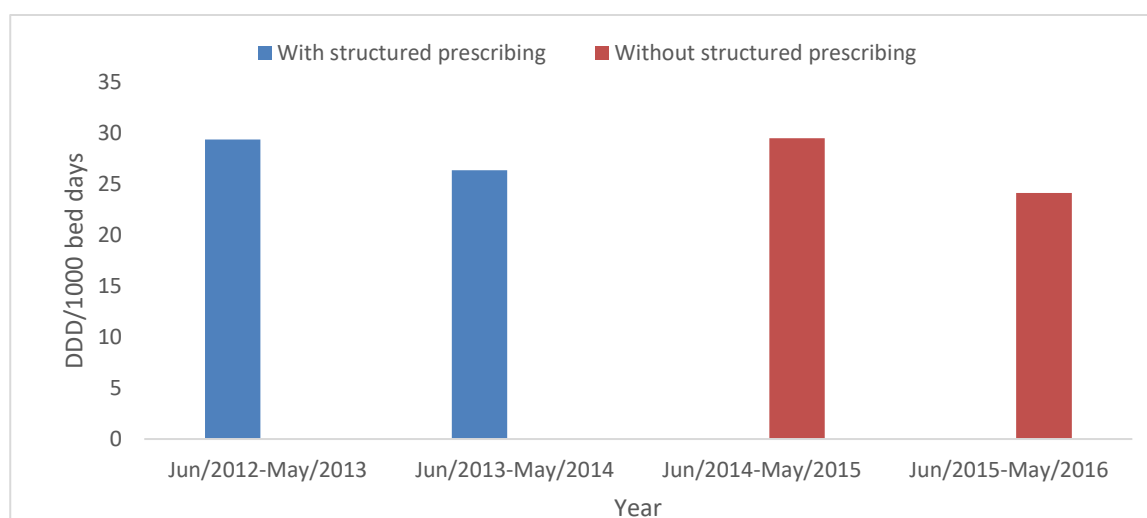
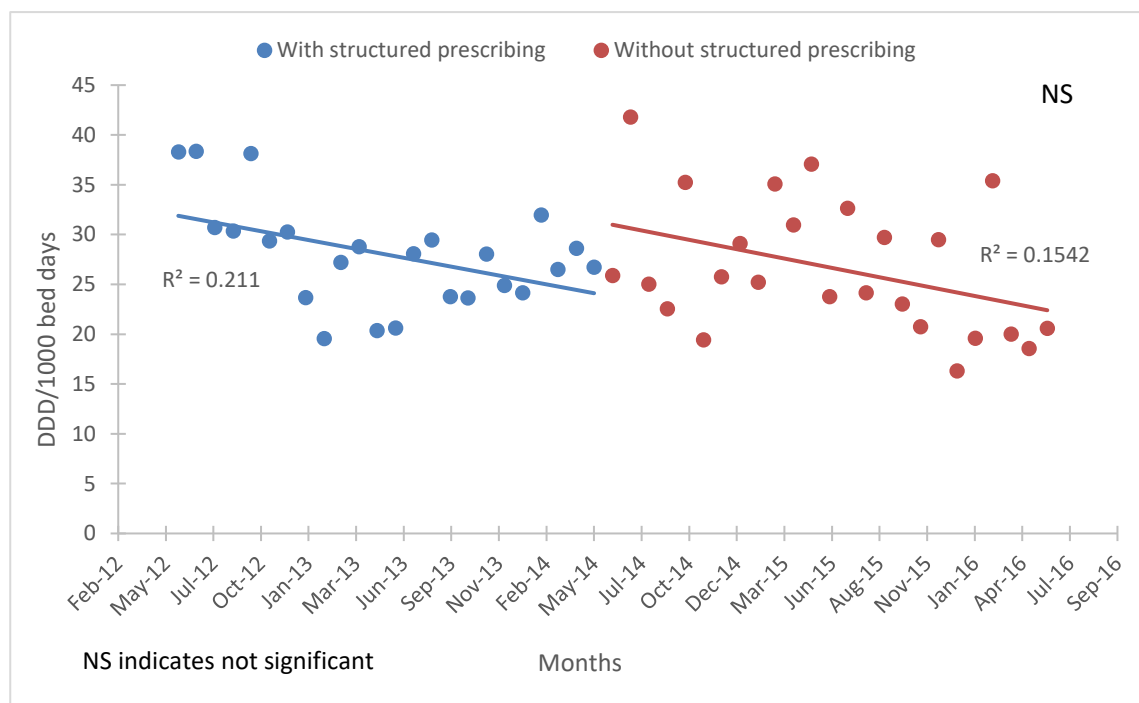


Figure 89: Monthly consumption of clindamycin reported as DDD/1000 bed days. Trend lines established by linear regression before and after deployment of structured prescribing are shown



6.14 Discussion

6.14.1 Rationale for the choice of exemplars

The exemplars were chosen to demonstrate the impact of structured prescribing on the quality of antibiotic prescribing. They include both broad and narrow spectrum antibiotics and some (amoxicillin and co-amoxiclav) are among the most commonly prescribed antibiotics at UHBFT. The main goal was to identify which agents were possibly affected by structured prescribing use and how. The antibiotic that was prescribed most commonly in each class of antibiotics was chosen to represent the whole category. Vancomycin was used as an exemplar because it is a broad-spectrum antibiotic and because of VRE (Vancomycin Resistant *Enterococci*). Evolution of microbial resistance to vancomycin is a growing problem, in particular, within hospitals. The increased use of vancomycin makes resistance to the drug worrying. Vancomycin can be given either orally or intravenously. It must be given intravenously for systemic infection because of its poor absorption from the intestine. Vancomycin must be given orally for treating pseudomembranous colitis. It must be given orally in

order to reach the site of infection in the colon. Carbapenems and quinolones were chosen as exemplars because they are broad-spectrum antibiotics and are associated with *clostridium difficile* infections. Ceftriaxone was chosen as an exemplar because it had the largest influence on cephalosporin use and is associated with *clostridium difficile* infections

6.14.2 The impact of structured prescribing on different exemplars

It has been shown that structured prescribing was associated with reduction in the use of most broad-spectrum antibiotics (such as co-amoxiclav, ceftriaxone and meropenem) and was associated with increase in the use of narrow-spectrum antibiotics (such as clarithromycin, doxycycline and gentamicin). The use of the broad-spectrum antibiotics examined increased in the period when structured prescribing was taken out of use. The use of narrow spectrum antibiotic alternatives decreased for the same period. The results suggest that structured prescribing achieved the goal of increasing the rational prescribing of antibiotics by curtailing the use of broad spectrum agents while promoting the use of narrow spectrum agents. The use of structured prescribing did not appear to be associated with any change in prescribing patterns of some antibiotics including rifampicin, clindamycin, clarithromycin and amoxicillin.

Structured prescribing was associated with increase in the use of ciprofloxacin and was associated with reduction in the use of levofloxacin. As both antibiotics are quinolones, this different impact is explained by policy or guideline enforcement by the structured prescribing system that favoured the use of ciprofloxacin over levofloxacin as the preferred choice taking owing to cost-effectiveness issues.

Structured prescribing was associated with increase in doxycycline use. This was expected as doxycycline is an alternative to amoxicillin according to the national guidelines. The use of amoxicillin varied during the periods with and without structured prescribing. It may be that some

patients were intolerant or allergic to amoxicillin which required switching to doxycycline for treating infections.

Structured prescribing is also associated with reduction in the use of meropenem. This control may help in maintaining options for treating multidrug resistant pathogens by reducing the potential for development of meropenem resistant organisms. Structured prescribing was associated with reduction in the use of ceftriaxone but its use increased steadily after structured prescribing was taken out of use. This could be related to hospital policy or may be because patients were allergic to other antibiotics or suffered from renal problems that required the use of ceftriaxone. Ceftriaxone does not need dose adjustment in renal failure and the increase in its use could be related to its pharmacokinetic profile and safety features in patients with renal failure.

Structured prescribing was associated with reduction in the use of broad-spectrum antibiotics such as vancomycin. This was coupled with the increased use of metronidazole during the period in which structured prescribing was used. Metronidazole is used as an oral treatment for *C.diff* instead of vancomycin and this clinical choice was promoted by structured prescribing owing to cost issues.

6.14.3 Other factors that affected structured prescribing

There are other factors that affected the way structured prescribing influenced antibiotic use within the hospital. These include seasonality changes affecting the incidence of specific infections to case-mix and staff turn-over. Patients may have had greater morbidity during winter months and needed more antibiotic therapy to treat their infections. There may have been fewer complex infection cases when structured prescribing was live and that could be why the use of broad-spectrum antibiotics was lower than expected during this period. The opposite is also possible which means that structured prescribing was effective in curtailing the use of broad spectrum antibiotics and directing therapy to narrow-spectrum antibiotics. An outbreak of a resistant pathogen such as *Pseudomonas aeruginosa*

or *Acinetobacter* may have required more intensive use of broad-spectrum antibiotics at any point during the four-year data analysis period. However, microbiology incident reports showed no outbreaks of resistant microorganisms over the four-year period. Therefore, structured prescribing was associated with reduction in the use of broad-spectrum antibiotics. Other factors include non-compliance of prescribers to structured prescribing recommendations because of the influence of more senior doctors who might overrule the recommended treatment proposed by the computer system. In addition, the system design meant that the use of structured prescribing was optional and it required a deliberate action by the user to access this element of the electronic prescribing system.

6.14.4 Usage trends for exemplars

The slope of the trend lines of antibiotic consumption for each exemplar varied during the periods with and without structured prescribing. For co-amoxiclav, both trend lines for the periods with and without structured prescribing had a positive slope, however, the slope of the trend line for the period without structured prescribing was steeper than the period with structured prescribing. This could mean that structured prescribing worked well and was associated with reduction in the rate of increase of use of co-amoxiclav during the period with structured prescribing. When CDSS was in place the total co-amoxiclav use for both of the years was lower with CDSS than without it. For ceftriaxone, both trend lines for the periods with and without structured prescribing had a positive slope, however, the trend line for the period with structured prescribing was steeper during the period with structured prescribing than the period without it. This could mean that structured prescribing increased the use of ceftriaxone during the period with structured prescribing. That would be a positive influence of structured prescribing on ceftriaxone consumption during the period with structured prescribing. Ceftriaxone usage as measured by DDD per 1000 bed days was lower with CDSS. For meropenem, the trend line for the period with structured prescribing had a negative slope compared to the trend line for the period without structured prescribing which had a positive slope. This could mean that

structured prescribing was successful in reducing the use of meropenem. When CDSS was in place the total meropenem use for both of the years was lower with CDSS than without it. For ciprofloxacin, the trend line for the period with structured prescribing had a positive slope compared to the trend line for the period without structured prescribing which had a negative slope. This could mean that structured prescribing encouraged the use of ciprofloxacin during the period with structured prescribing. That would be an indication of a positive influence of structured prescribing on ciprofloxacin consumption during the period with structured prescribing. When CDSS was in place the total ciprofloxacin use for both of the years was higher with CDSS than without it.

Specific conclusions

- ✓ Structured prescribing was associated with reduction in the use of broad-spectrum antibiotics
- ✓ Structured prescribing was associated with increase in the use of narrow spectrum antibiotics
- ✓ The rate of antibiotic consumption increased during structured prescribing more rapidly than after withdrawal but the overall usage of antibiotics was greater after withdrawal
- ✓ The overall usage of antibiotic and the overall rate of change are dependent upon the changes contributed by each antibiotic making up the overall consumption of antibiotics.

Chapter 7: General discussion

7.1 General discussion

In this section, the research findings are summarised, and the implication for research, practice and future work are discussed. A number of gaps in the literature on the impact of CDSS on antibiotic use in hospitals in the UK have been identified. These gaps range from the impact of CDSS on antibiotic in hospitals and the sociotechnical factors required for the success of CDSS implementation. The present research has sought to address some of these knowledge gaps. The aims and objective of this research have been addressed through the completion of three strands of work including the completion of a systematic review and meta-analysis to examine the evidence of the impact of CDSS on antibiotic use in hospitals. This was followed by a qualitative study using a questionnaire to explore the perceptions and attitudes of senior and junior healthcare professionals towards CDSS. Finally, a quantitative before and after study was completed to examine the impact of CDSS on the volume of antibiotic use in the form of defined daily doses. The key findings of the research are described, consideration is given to the strengths and weaknesses inherent in the work and policy implications arising from the findings are considered.

7.2 Main findings

7.2.1 Systematic review and meta-analysis (Chapter 3)

The systematic review and meta-analysis reported in chapter 3 developed a comprehensive search strategy to locate 81 high quality research articles investigating the impact of CDSS on antibiotic use in hospitals. A quality assessment tool was adopted in order to evaluate studies examining the impact of CDSS on antibiotic use in hospitals. From the results forest plots were created to illustrate the impact of CDSS on patient-related outcomes and practitioner performance. The formative work of the systematic review and other work packages clearly showed that CDSS was perceived as a tool having the potential to optimise the use of antibiotics internationally. Perhaps more importantly, CDSS was perceived as a tool to improve clinical practice and help to contain antimicrobial

resistance. However, one of the main findings of the systematic review was the lack of evidence of an impact of CDSS on patient related outcomes.

The process of identifying, critically appraising and synthesising the evidence was challenging. The initial search of the literature revealed that the research articles identified were poorly indexed in medical databases. A novel search strategy was developed to identify the literature by using several key words in different cycles to locate as many related research articles as possible.

Quality assessment of the literature was also challenging. There are many quality assessment tools available to examine literature but the majority were not applicable given the varied study design of included research studies in particular non-randomised controlled studies. The quality assessment tool has been used in systematic reviews by Garg and co-workers (Garg et al., 2005) and Hunt and co-workers (Hunt et al., 1998). The quality assessment tool was found to be suitable for the needs of the present research because it covered a wide range of methodological approaches including non-randomised studies and was suitable given the poor quality of the included studies. The tool included five domains: method of allocation, unit of allocation, presence of baseline difference between groups, objectivity of outcomes and completeness of follow up.

The systematic review outputs showed that there was a growing environment of using CDSS in healthcare. The systematic review examined the impact of CDSS on several outcome measures. The findings showed that the use of CDSS could improve the adequacy of antibiotic coverage for empirical treatment by more than 100%. Assessment of appropriate antibiotic use was based on the adequacy of antibiotic coverage. Studies often neglected to include details of how and by whom appropriateness was determined. Appropriateness includes several dimensions such as compliance to guidelines, an appropriate choice of antibiotics and an appropriate dose. In many studies, it was not clear how many of these factors were considered when discussing appropriateness.

The findings from 20 studies from the systematic review also showed that CDSS lowered mortality by 15%. CDSS was also successful in improving adherence to evidence-based guidelines. The finding showed that the impact of CDSS in curtailing the cost of treatment and length of stay of patients was conflicting. The reason for these conflicting results was because the cost and length of stay were reported in different currency units and different lengths of stay.

The quality of the included studies together with their study designs was very poor which further complicated the present systematic review. The variety of outcome measures used was another obstacle as few studies reported their results using the same outcomes. Seven outcome measures were evaluated and the number of studies evaluating the same outcome but using different measures was high which further complicated the analysis and made conducting meta-analysis problematic. Antimicrobial resistance was one of the outcomes that was poorly evaluated given the low number of studies (2 studies) assessing it.

The majority of CDSS tools evaluated in the present systematic review were home-grown and developed in academic medical centres by researchers who used these tools rather than commercially available software packages. This increased the chances of bias and conflicts of interest as these systems were evaluated by the researchers who created them. The findings for the most part came for home-grown CDSS, and it is not known how these tools would operate if deployed in other environments. The differences between our systematic review and other systematic reviews that addressed a similar research question are the type of outcomes evaluated. Our study evaluated seven outcomes while the study by Baysari and co-workers evaluated three outcomes (appropriateness of antibiotic use, mortality and length of stay) (Baysari et al, 2016). Our systematic review findings and the findings of Baysari overlap that CDSS improved the adequacy of antibiotic coverage. Our systematic review differs from Baysari study that CDSS lowered mortality by 15% while their study

found no effect on mortality. Other systematic reviews evaluated the impact of CDSS on practitioner performance and process level outcomes.

7.2.2 Online Questionnaire (Chapter 4)

Inadequate attention has been paid previously to socio-techno-cultural considerations in relation to the use of CDSS. The present systematic review showed that the majority of CDSS recommendations are ignored by end-users. Therefore, it was logical to use a questionnaire as part of the present studies in order to explore the perceptions and attitudes of medical and non-medical health care professionals towards CDSS. Creation of the questionnaire was challenging because it was not known what type of questions will meet the study objectives, aims and research questions. The creation of the questionnaire was based on literature of previous work related to the research questions. The questionnaire was piloted among a group of pharmacists who filled it in on the early phases of the questionnaire development. One of the recommendations from CDSS that is overlooked or ignored by users are alerts for example drug interaction alerts. Although such alerts are very important, findings from the present systematic review showed low adoption rates of such alerts and most of them were overlooked. Prescribers' awareness of an issue called alert fatigue might precede whether the CDSS recommendations are followed. Adequate and ongoing training is required to ensure ease of use and that maximum benefit from CDSS is obtained for prescribers. Although self-reported perceptions of participants ranged from reluctant to enthusiastic, an enthusiastic perception prevailed evidenced by their previous use and exposure to CDSS and their willingness to use CDSS. Participants were determined to realize the benefits of CDSS. Efforts can be directed to fulfil all the required needs and inclusion of preferred features in designing a CDSS identified in the questionnaire results. But still users may not use the CDSS system if such use is optional. This could be explained owing to issues related self-autonomy or influence of superiors. Junior doctors may be strongly

influenced by their senior's decisions and override CDSS recommendations especially in severe cases of infections and complicated cases.

The psychosocial determinants of acceptance of CDSS recommendations have remained poorly understood. In a study by Chow and co-workers, the facilitators for the adoption of CDSS recommendations were willingness to accept CDSS recommendations, trust of CDSS recommendations and usefulness of CDSS recommendations (Chow et al., 2015). The barriers for the adoption of CDSS recommendations were personal or team preference and patient factors. Factors determining the acceptance of CDSS recommendation were different between senior and junior doctors. If a CDSS system was designed with all features identified in the present online questionnaire, the participants may not use it or they may not adopt its recommendations. This could be due to a lack of credibility of the CDSS or influence of superiors or may be a reluctance to rely on CDSS in clinical practice. Prescribers are in a situation that they may embrace CDSS but still question its credibility and effectiveness in clinical practice. The questionnaire results identified that senior doctors showed more positive views than junior doctors. In contrast, Chow and co-workers showed that senior doctors were more resistant to CDSS recommendations than junior doctors (Chow et al., 2015). Junior doctors in the present online questionnaire were more willing to accept CDSS recommendations as they perceived it as a way to strengthen their knowledge and experience.

In a UK study which identified the determinants of prescribing etiquette of antibiotics (Charani et al., 2013), the effectiveness of hospital guidelines aimed at optimising the prescribing behaviours of junior doctors was limited because of the social norm of prescribing etiquette set by senior doctors. CDSS could be enhanced by understanding the reasons for non-acceptance of hospital prescribing guidelines by senior doctors. However, in the present online questionnaire, senior doctors were willing to accept and use guidelines. Senior doctors depend on their own clinical knowledge and

experience to decide which antibiotic needs to be prescribed. Some clinicians find protocols and guidelines too restrictive for individual patient use.

Table 21: Rules of antimicrobial prescribing etiquette

No interference with prescribing decisions of colleagues
Accepted non-adherence to policy
Hierarchy of prescribing: Junior doctors do the prescribing process but senior doctors decide what needs to be prescribed

Adapted from (Charani et al., 2013)

Ten questions were created in the present online questionnaire to explore CDSS users' perceptions and attitudes and the focus was to explore awareness of CDSS, awareness of the benefit of information technology, awareness of the decision support functionality of the electronic prescribing used, clinical information needs when prescribing antibiotics and perceived and preferred features of CDSS.

The main findings of the questionnaire showed there were varied perceptions and attitudes towards CDSS. The majority of participants were aware of the potential benefits of CDSS in optimising prescribing decisions. A small number of participants were not aware of the potential benefits possibly because they felt they had received sufficient training and so did not need to use CDSS or because their educational curricula and training courses have not focussed on electronic prescribing and CDSS. Almost half of participants had previous experience in using CDSS and the others had never used CDSS. This is because electronic prescribing and clinical decision support is not in place in every hospital in England and junior medical staff change jobs every six months and come from different backgrounds.

Many respondents understood the potential benefit of CDSS and could list clinical benefits of using it. These range from better access to information and greater efficiency and improved safety of work. However, these responses were paralleled by anxiety of the CDSS as a new system that may introduce errors and affect patient outcomes. In the systematic review, the efficacy of CDSS in improving the appropriateness of antibiotic prescribing and reducing mortality was identified which is objective albeit low quality evidence that the fear of these prescribers is unfounded. Participants may be worried that using CDSS may lead to spending less time with patients leading to adverse patient outcomes.

CDSS are not a standalone application and their successful operation requires changed practice and integration with other clinical and health information systems. Participants may be concerned about the ability of CDSS to help in the delivery of care to patients and this is accompanied by anxiety whether the new CDSS will work. They may be worried that the use of a new technology such as CDSS will impair the existing environment of communication with other health care professionals as they will communicate through computers. These fears can only be countered by thorough training and change management before such systems are introduced.

Participants may be worried that they will not be able cope with CDSS and the changes it might introduce to their practice. This further exacerbates their anxiety about using it. This is also related to lack of adequate training and support. Success of CDSS implementation required a high level of collaboration between relevant departments and staff to ensure that they are able to use the new system effectively and if they have any problems they will be supported.

Some participants recommended that the prescription history of previous antibiotic treatments be accessible which would save time and give the prescriber an overview of which antibiotics have been given previously which would facilitate the prescribing of appropriate antibiotics. Different features were identified as being required by the participants, the main feature being the ability to suggest a

therapeutic regimen. It is not surprising that this was the most requested feature because prescribers want to prescribe the correct regimen and avoid any errors. The ability to display treatment guidelines was among the other features required of the CDSS. Junior doctors also are influenced by their superior in their decisions and that makes it difficult for them to comply with prescribing guidelines suggested by the CDSS. Prescribing according to guidelines is important in both curtailing the cost of treating infections and containing AMR. However, prescribers do not always follow guidelines and it is vital to answer why they do not. Other perceived preferred features were the ability to monitor side effects and highlight drug-drug interaction plus the electronic prescribing system must operate at comparable speed with handwriting prescription so that it does not take more time to prescribe for the patient.

7.2.3 Quantitative study (Chapter 5)

Few studies in the systematic review reported on the impact of CDSS on the volume of antibiotics used which made subsequent meta-analysis problematic. The volume of antibiotic prescribed was reported in different units, which further complicated the analysis. It was decided to conduct a quantitative study to examine the impact of CDSS on the volume of antibiotic use expressed in DDD/1000 bed days. Defined daily doses was used because it is WHO and it is the most commonly used metric for measuring the volume of antibiotic use. Structured prescribing at the study hospital went live in June 2008 and was taken out of use in June 2014. A retrospective before and after study design was adopted because it is less expensive, it is conducted on a smaller scale and it requires less time to complete. Therefore, it was decided to undertake a retrospective before and after study comparing the volume of antibiotic use in the periods with structured prescribing and without. Obtaining the data from the hospital was protracted initially and the first draft of the data received was complicated and difficult to use because it was unstructured and disorganised. The first draft presented each antibiotic separately which made grouping the antibiotics problematic and time

consuming. Antibiotics were grouped according to the BNF classification and they were among the most commonly prescribed antibiotics at UHBFT. A second dataset contained data which included the number of dose units used. The data presented was comprehensive for all antibiotics used at the hospital over the four-year study period. The findings from the quantitative study were varied according to the class of antibiotic but overall, structured prescribing had one of three general effects on the different antibiotics used:

- Structured prescribing had a positive impact and reduced antibiotic volume of use
- Structured prescribing had a negative impact and increased antibiotic volume of use
- Structured prescribing had a neutral effect and caused no change on antibiotic volume of use.

Structured prescribing had a positive impact and reduced the quantity used of the following antibiotic classes: cephalosporins, carbapenems, sulfonamides, and glycopeptides. It had a negative impact and increased the quantity used of the following antibiotics including aminoglycosides, tetracyclines and antimycobacterials. It also had a neutral impact on penicillins, macrolides, quinolones, and miscellaneous antibiotics.

The deployment of the CDSS was associated with changes in the patterns of consumption of broad spectrum antibiotics. The limited use of broad-spectrum antibiotics appeared to encourage the greater use of narrow spectrum antibiotics where possible. In the case of cephalosporins and carbapenems, structured prescribing was successful in reducing their use. This appears to have led to an increased use of other alternatives namely aminoglycosides and tetracyclines with a narrower spectrum of activity. It would appear that these effects were influenced by guidelines and policies of the hospital when the structured prescribing system was live. The use of penicillins remained stable which could be explained by an institutional policy for treating patients with febrile neutropenia with co-amoxiclav for low risk patients or piperacillin/tazobactam for high risk patients during both periods with and

without structured prescribing. There were no reports of any outbreak of multidrug resistant pathogens during the period when structured prescribing was live that may have required the use of certain antibiotics which may have affected the impact structured prescribing system. Therefore, structured prescribing reduced the use of broad spectrum antibiotics. The use of aminoglycosides was encouraged and increased in the period when structured prescribing was live. Structured prescribing may have preferred the use aminoglycosides over penicillins or cephalosporins despite aminoglycosides toxicity in treating specific diseases. Structured prescribing was used to promote these new antibiotic guidelines and protocols and directed physicians towards recommended antibiotics at the time of antibiotic prescription.

Both aminoglycosides and tetracyclines were prescribed as alternative treatment to penicillins, cephalosporins and carbapenems recommended by the structured prescribing system. Structured prescribing appeared to be associated with success in reducing the use of most antibiotics except for aminoglycosides, tetracyclines and antimycobacterials. Structured prescribing preferred prescribing narrower spectrum antibiotics (tetracyclines) over broad-spectrum alternatives for mild cases of infection and this is evident by the reduction in prescribing cephalosporins, quinolones and carbapenems.

Structured prescribing appeared to be associated with success in reducing the use of broad spectrum agents such as meropenem, vancomycin, ceftriaxone and levofloxacin. This decrease was coupled with an increase in use of narrower spectrum antibiotics such as gentamicin, metronidazole and doxycycline. Structured prescribing had no effect on amoxicillin, clarithromycin, rifampicin and clindamycin. The main goal of structured prescribing was to promote use of narrower spectrum alternatives for treatment of infection and reduce the use of broad spectrum antibiotics. It is possible that the impact of the structured prescribing system was influenced by other factors that prevented maximum benefits being realised from its use. This could be because of the prescribing etiquette of

antibiotics set by senior doctors and followed by juniors which entails prescribing broad spectrum antibiotics in severe cases. It is possible that increased numbers of patients with severe infections were treated during the period when structured prescribing was operational and this made the following of the recommendations from the structured prescribing system problematic. For example, in patients with sepsis, broad spectrum antibiotics need to be prescribed and the earlier broad-spectrum antibiotics are prescribed there is more likelihood of treatment success. Clinicians may have found structured prescribing recommendations not suitable for certain infections and that is why they overlooked structured prescribing recommendations. Clinicians have their own experience and may be their experience conflicted with structured prescribing recommendations.

Other factors that may have influenced the way structured prescribing worked include staff turn-over. The application of adequate training may have been inconsistent. This could be due the limited opportunity to attend training sessions that are held at fixed times each year. This is a situation where structured prescribing existed but the new staff were inadequately trained. There is a possibility that staff were not aware of the presence of structured prescribing at all. Therefore, adequate training should be enforced quarterly or on the arrival of new junior doctors. Junior doctors need to learn how to use the system and understand what decision support functionality structured prescribing is capable of. This could be reflected in the responses of junior doctors in the questionnaire which showed low level of interest in using electronic prescribing and CDSS.

It is possible that the effect of structured prescribing was influenced through rapid appearance of clusters of infected patients (an epidemic). An outbreak of infections of multidrug resistant organisms may have led to prescribers not following structured prescribing recommendations. A new policy could be launched to contain an outbreak without recommendations being reflected in CDSS protocols. An outbreak of *Clostridium difficile* for example may have required the use of vancomycin instead of metronidazole. Structured prescribing recommendation for *Clostridium difficile* infection

was metronidazole, but because of the severity of the outbreak, vancomycin was prescribed instead. However, based on data from the microbiology department no outbreaks occurred during the periods with and without structured prescribing so this possible explanation may be discounted.

The slope of the trend lines of antibiotic consumption varied during the periods with and without structured prescribing. The rate of antibiotic consumption increased during structured prescribing more rapidly than after withdrawal but the overall usage of antibiotics was greater after withdrawal. The overall usage and the overall rate of change are dependent upon the individual changes from each antibiotic contributing to the overall use. There is a possibility that there were other factors that influenced the use of antibiotics (formulary, government plans, seasonality changes, case mix and staff turn-over). The cases where the slope of the data shows a steeper rise when CDSS was live may have been because the system was encouraging users to use that particular family of antibiotics. That would be an indication of the positive influence of structured prescribing in changing prescribing patterns. There is another possibility that the system was not actively promoted and so other factors might have impacted on use such as case mix which is not a factor which was examined. For all antibiotics structured prescribing increased the use of some antibiotics due to a hospital policy and that would be an indication of a positive influence of structured prescribing on antibiotic consumption. However, for both of the years when CDSS was in place the total antibiotic use was at a lower level than without it. Antibiotic usage as measured by DDD per 1000 bed days was lower with CDSS.

Gonorrhea is becoming difficult to treat as many antibiotics are losing their potency because of the misuse and overuse of antibiotics. The bacterium *Neisseria gonorrhea* has developed resistance to ciprofloxacin, cefixime and ceftriaxone. Gonorrhea is resistant to quite a lot of antibiotics and has developed resistance to new antibiotics rapidly including ceftriaxone (Unemo and Shafer 2011). The

problem is that prescribers are prescribing the wrong antibiotics for treating gonorrhea. Some patients may respond to the antibiotic and some patients may develop resistance and the disease may be disseminated. Cefixime is no longer effective against *Neisseria gonorrhea*. There is a need to conserve the efficacy of existing antibiotics and prolong the use antibiotics for treating gonorrhea. There is also a need to promote antimicrobial stewardship for the antibiotics we have and making sure that we are not treating patients with drugs where there is high level of resistance. For treating ceftriaxone-resistant *Neisseria gonorrhea*, multiple dosing or using a higher dose is recommended. A better approach would be to use combination of antibiotics to have a synergistic effect. Combination of antibiotics may be effective even if the pathogen is resistant to each antibiotic separately. However, combination of antibiotics would be a problem for less resourced settings. Action should be taken in the form of joint effort of governments, industry, academia and health establishments to address the problem of resistance to gonorrhea. The emergence of *Neisseria gonorrhea* resistant strains to ceftriaxone should be a wake-up call. In the meantime, to reduce the spread of resistance, active surveillance systems should be strengthened globally, nationally and at a local level.

7.3 Strengths and weaknesses

7.3.1 Systematic review

A comprehensive search strategy and a search of grey literature was carried out together with hand searching of bibliographies of included articles in order to identify as many studies as possible to enrich the level of evidence acquired. The output has importance for policy and research agendas because it provides a platform of evidence of the benefit of CDSS found in secondary care. The systematic review of the literature examined clinical outcomes and other aspects of end user satisfaction with CDSS tools

There are limitations of the systematic review including the primary focus on quantitative studies. Given the importance of qualitative studies in understanding the findings from quantitative studies, it is important to incorporate qualitative studies in any analysis. Although the systematic review adopted a broad systematic approach, the lack of qualitative studies found made it less comprehensive than it might have been.

Comprehensive key terms were adopted in order to locate studies, however, other studies indexed under different key terms may have been omitted. Therefore, the search strategy was very comprehensive in order to locate studies indexed under different key terms. Non-English literature was also excluded which might have included studies of good quality that may have enriched the level of evidence acquired.

7.3.2 Online questionnaire

One of the strengths of the questionnaire study was that it examined the perceptions and attitudes of healthcare professionals towards CDSS use specifically in relation to antibiotic prescribing. It is among the few studies that explore qualitative measures as the majority of published literature focussed on examining the effectiveness of CDSS on specific qualitative outcome measures. The likelihood of bias was reduced given the fact that respondents were from different backgrounds and of different grade. The population of the online questionnaire was homogenous and included participants with different grades and experience. The low response rate (6%) for the questionnaire is a limitation of the work. Efforts were placed to increase the response rate by sending the questionnaire two times with two reminders. However, it was not possible to identify the reasons for the non-completion of the questionnaire.

7.3.3 Quantitative study

A number of reports have examined the consumption of antibiotics in the whole of England over time without incorporating the impact of electronic prescribing and CDSS on the volume of consumption.

The present study examined the impact of structured prescribing on a wide range of antibiotics which add to the strength of the work.

A limitation of the quantitative study was the lack of a control group. This may have reduced the strength of the study and introduced an element of bias. Another weakness was the short duration of time that the study covered being two years with CDSS and two years without CDSS.

7.4 Implication for policy, practice and research

The programme of work has contributed to the body of evidence that antibiotics continue to be poorly prescribed and showed limited adherence to guidelines. The programme of work provided an overview of the evidence of the impact of CDSS on antibiotic use and explored the perceptions and attitudes of health care professionals towards these tools. The programme of work also quantified the impact of CDSS on the volume of antibiotic use expressed as defined daily dose per 1000 bed days.

7.4.1 Policy

CDSS design and development is not regulated in either the US or the UK (Sheikh et al., 2011). The cost of developing and maintaining these application is high. So, it is very important to be able to share the content of CDSS within and across organisations and make them tailored to an NHS context. This will reduce the cost of running these systems. It is important to ensure interoperability between CDSS applications across the NHS. The majority of IT applications currently in place are not interoperable which makes sharing of information problematic. NHS Connecting for Health has been active in promoting interoperability and content sharing of CDSS tools and these efforts should be maintained (Sheikh et al., 2011).

The quality of data entry by healthcare professionals should be scrutinised for correctness and completeness in order to maximise the benefit of using CDSS as any recommendations given will be

dependent of the quality of the data entered. If the data entered was incorrect or incomplete, the recommendation given may ultimately be incorrect and potentially dangerous. The completeness and correctness of data entry is crucial for the secondary uses of data. For example, if a patient with pneumonia was allergic to penicillins, and this piece of information was not entered into the system, then the recommendation provided may include prescribing penicillins and this may subsequently cause harm to the patient.

CDSS are being adopted within the healthcare arena and are being used in different health care sectors. It is important to know how these systems are implemented and deployed in order to maximise the long-term benefits. These systems need to be evaluated regularly and updated based on the outcome in order to match healthcare needs. It is necessary to learn how to introduce CDSS effectively and how to improve them once implemented. The National Programme for Information Technology (NPfIT) has been a leader in implementing and continuously modifying and upgrading CDSS specifications in order to supply the NHS with effective CDSS tools that will meet healthcare needs (Sheikh et al., 2011).

There is a need for more comparative studies in relation the use of CDSS in order to facilitate decisions relating to procuring CDSS systems. Randomised controlled trials are the gold standard for evaluating interventions but have not been applied to HIT which is hard to understand. It is difficult to utilise RCT to evaluate CDSS because of the risk of contamination or bias but this should not deter research in this area of practice. Alternative methodologies could be applied in such evaluations. The stepped-wedge method is one of the study designs that may be utilised to assess HIT interventions and CDSS. Stepped-wedge randomised trial design involves sequential rolling out of an intervention over time where the participants will have received the interventions in different time periods at a random order (Brown and Lilford, 2006). Commercial and home-grown CDSS tools should undergo such evaluation. There is a need to form regulatory bodies that assess these applications to ensure that

they are in line with quality and safety standards of HIT interventions. This could take the form of an accreditation system.

As HIT has an impact on the daily working practice of healthcare professionals. There is a need to both educate and train health care professionals in how to use and interact with HIT interventions effectively. Such training should start from education curricula during university training and extend through their working careers.

There is a need for international collaboration to embrace and develop the role of HIT in health care practice. This shared interest provides a platform for sharing lessons and experiences gained when deploying CDSS tools. Such learning is currently not shared widely and there is duplication of effort in some areas with large gaps in other areas. Such international collaboration could help in developing effective CDSS tools and evaluating such tools in a generalizable way.

7.4.2 Practice

There is a possibility that the benefits of using CDSS will be directed to practitioner performance and process level rather than improving patient outcomes. CDSS can be beneficial in improving the way antibiotics are prescribed and in optimising practitioner performance and guideline adherence. Therefore, it is very important to scrutinize CDSS tools before investing in these technologies. More importantly, there is a need for clinical scrutiny in order to establish in which areas of practice CDSS will be beneficial rather than them being considered as a technology deployed for technology sake.

7.4.3 Research

A number of questions have remained unanswered that warrant further investigation in the future. It is important to know in which contexts CDSS can be beneficial for patient level outcome measures. The development and deployment of CDSS is very expensive both financially and in human resources so it is crucial to understand the economic consideration associated with deployment of CDSS tools

given the current financial environment. There is a need to assess clinical patient outcomes and these need larger studies of patients being followed up for a number of years in order to have suitably high-powered studies. Such high-powered studies will enable meta-analysis of patient related outcomes and enrich the level of evidence.

7.5 Future work

CDSS have many benefits and provide the potential to optimise the way antibiotics are prescribed. However, as demonstrated by this programme of work, there remains a wide gap between these potential benefits and the realisation of actual benefits of CDSS in optimising antibiotic use. This could be explained by the few evaluations which have been published when compared to the wide development and deployment of these tools. This gives the indication that the benefits of CDSS might be considered to be self-evident and that no evaluations for these tools are required.

Building on the findings from the systematic review conducted in the present work, it may be concluded that the quality of included studies was still inadequate to produce high quality evidence for healthcare professionals and policy makers.

The lack of economic evaluation of CDSS is a limitation of the current work given the high cost of developing and running these tools. The quality of economic analysis of CDSS tools has been low. The present systematic review contained mainly before-and-after study designs and failed to identify any cost-effectiveness analyses.

More studies are required on the organisational impact of CDSS such as impact on workflow, efficiency and psycho-social and socio-technical-cultural consideration. This type of evaluation is uncommon as most researchers tend to focus on the clinical impact of CDSS. Evaluating the organisational impact of CDSS is complementary to clinical and cost-effectiveness evaluations. Related issues to the organisational impact are the timeliness and the time period over which these

evaluations were conducted. As technology advances rapidly, evaluations may become less relevant. The detection of the benefits and risks may be incomplete with evaluation of short periods of time. Therefore, it is suggested that research into the development of the clinical, organisational and economic impact of CDSS would make future work more informative.

The questionnaire conducted for this thesis was successful in exploring the perceptions and attitudes of some users towards CDSS. However, more qualitative work is needed to obtain results from larger sample sizes that are more conclusive. Additional qualitative work in the form of focus group interviews or in-depth interviews are needed to enrich the evidence and to better understand how users perceive CDSS and to reflect on the development, design and deployment of CDSS tool. Other future work should include a systematic review of qualitative studies in order to produce a robust evidence related to behavioural issues and attitudes.

The quantitative work package from the present study was successful in demonstrating the effect of CDSS in curtailing the volume of use of antibiotics. However, the failure of incorporating contextual factors when conducting CDSS evaluation has remained a major problem. Qualitative work is still not incorporated with quantitative research. There is a need to conduct mixed method approaches in order to understand the contexts in which CDSS applications operate. Quantitative findings need to be understood in the context in which CDSS tools are implemented and evaluated.

There is a need for education and training of end users in use of information technology. There is also a need to increase the level of competency of end users in using sophisticated CDSS tools in order to maximise benefits. In order to achieve this, the education curricula need to be tailored to educate healthcare professionals about information technology during their undergraduate programmes. Seminars and training courses should be designed to make end users more competent in using CDSS tools.

7.6 Conclusion

The findings from this programme of work can be used to enrich the debate around the impact of CDSS on antibiotic use. The systematic review demonstrated the efficacy of CDSS in improving the adequacy of antibiotic coverage across different settings. However, evidence on the effect of CDSS on clinical and economic outcomes and volume of antibiotic use was limited. CDSS appears to be safe because the systematic review did not show any significant risks such as worsening mortality or increased length of stay. Widespread uptake of CDSS will require a better understanding of the nature of information included, when and how it should be delivered and what format of delivery should be used. A critical evaluation of any adverse consequences is very important to provide a complete understanding of the challenges of CDSS implementation. The majority of studies identified were conducted in the United States which means that the generalizability of any reported successes of CDSS is difficult. In addition, the types of setting in which CDSS systems were developed and implemented were limited. CDSS presents a promising future for optimising antibiotic use and improving patient care. However, in order to reach firm conclusions about the impact of CDSS on antibiotic use, more high-quality studies are needed within different settings and in different healthcare systems.

The findings from the questionnaire responses provided a varied range of user perceptions and attitudes towards CDSS. Consultant grade medical staff were interested in deploying and adopting CDSS recommendations and they showed a high level of awareness and willingness to adopt CDSS. Junior doctors, to a lesser extent were aware of CDSS and were likely to adopt CDSS recommendations. Varied clinical information needs and perceived benefits were evident from the questionnaire on participants grade and speciality.

The quantitative study was effective in demonstrating the impact of structured prescribing on the volume of antibiotic use. Structured prescribing had positive, negative and neutral effects on different

classes of antibiotics. Structured prescribing was successful in reducing the total volume of antibiotic use by a mean difference of -110.14 DDD/1000 bed days, ($p=0.26$). When structured prescribing was removed the total use of antibiotics increased by 13.1% from 1436.3 in June 2012 to 1624.85 DDD/1000 bed-days in June 2016. This gives an indication that structured prescribing had an impact and that it should be relaunched after modification and upgrading in order to match its functionality to end users' needs and identified beneficial features.

Despite efforts being made to computerise clinical practice and supply clinicians with tools and rules to facilitate their clinical practice, clinicians have their individual unique way of practice. They rely on their evidence-based experience in taking decisions and do not prefer to be guided by anything whether it is a computer-based or paper based assistance. They consider themselves autonomous but in reality, they are governed by organisational restraints.

Specific conclusions:

- The findings from the systematic review showed that CDSS improved the adequacy of antibiotic coverage for empirical treatment by more than 100%.
- The findings from the systematic review showed that CDSS could lower mortality by 15%.
- The majority of participants who responded to the questionnaire supported the role of IT and acknowledged its role in optimising the use of antibiotics.
- The majority of participants who responded to the questionnaire were aware that the electronic prescribing system in use was capable of providing clinical decision support functionality.
- Senior doctors who responded to the questionnaire showed more positive attitudes towards CDSS than junior doctors
- CDSS appears to be accepted widely.
- Structured prescribing reduced the total use of antibiotics by a difference of means of

-110.14 DDD/1000 bed days, $p=0.26$. This is because structured prescribing was implementing a trust policy

- Clinicians are independent in prescribing antibiotics and they depend on their evidence based practice rather than guidelines or decision support tools.

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